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New Directions in the Heck Reaction

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Written by:

Matthew McConville

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New Directions in the Heck Reaction

Matthew McConville

Abstract: The Heck reaction of electron-rich olefins differs from that of electron-deficient in that the regioselectivity of the reactions is often lower and more difficult to control. Recent work has shown that a variety of methods can be employed to control the regioselectivity when olefins such as enol ethers, hydroxylalkyl vinyl ethers, N-vinyl amides, unsaturated alcohols and vinyl silanes are subjected to arylation/vinylation conditions. The work in this thesis describes expansion of the Heck chemistry of electron-rich olefins. This was achieved in several ways, including application of catalysts not normally considered useful in these reactions and application of established catalysts to new processes.

Chapter 2 describes the investigation of the Heck vinylation of electron-rich olefins with vinyl halides. Although relatively unexplored, vinylations are usually treated as analogous to arylations. We found some striking differences between the two reaction sub-types and as a result we found a catalytic system comprising a Pd-hemilabile phosphine system that greatly improved the efficiency of the reaction and allows smooth vinylation of otherwise difficult 2-substituted vinyl ethers. Following on from this a mechanistic investigation revealed that it is likely the Heck vinylation follows a neutral pathway as opposed to the generally accepted ionic pathway.

In Chapter 3 we report that the Heck reaction of alkyl vinyl ethers in diols leads directly to cyclic ketals. Replacing the expensive hydroxy alkyl vinyl ethers with butyl vinyl ether greatly reduces the cost of the reaction and allows chemoselective ketal formation in the presence of other carbonyl functionalities. Both the aryl group and the ketal ring can be varied by choosing the appropriate aryl bromide and alcohol solvent. We also describe a phosphoric acid catalysed ketalisation of isolated enol ethers in alcohol solvents that allows diols not suitable for the Heck reaction to be incorporated into the products, again in a chemoselective fashion.

In Chapter 4, the regioslelactive arylation of unsaturated alcohols is utilised in a one pot procedure for the synthesis of substituted tetrahydrofuran and tetrahydropyran derivatives. Previous methods for the arylation of unsaturated alcohols were unsuitable for the one pot procedure and it was found that H-bond donating ammonium salts could affect regiocontrol whilst still being compatible with the acid-catalysed cyclisation. A range of aryl bromides were successfully converted to the corresponding 2-aryl-2-methyl saturated oxygen heterocycles using the new procedure.

Definitions and Abbreviations

%	percent
α	alpha
β	beta
δ	chemical shift (delta)
API	active pharmaceutical ingredient
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
[bmim] [BF_4]	1-butyl-3-methylimidazolium tetrafluoroborate
[bmim] [PF_6]	1-butyl-3-methylimidazolium hexafluorophosphate
bn	billion
Boc	*tert*-Butyloxycarbonyl
^{n}Bu, Bu	*n*-butyl
^{t}Bu	*tert*-butyl
BVE	butyl vinyl ether
°C	degree celsius
^{13}C	carbon-13
CI	chemical ionization
Conv.	conversion
Cy	cyclohexyl
d	day(s)
d	doublet
DCM	dichloromethane
DFT	Density functional theory
DIPEA	*N,N*-diisopropylethylamine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulphoxide
DPPB	1,3-bis(diphenylphosphino)butane
DPPE	1,3-bis(diphenylphosphino)ethane
DPPF	1,1'-bis(diphenylphosphino)ferrocene
DPPM	1,3-bis(diphenylphosphino)methane
DPPP	1,3-bis(diphenylphosphino)propane

d.r.	diastereomeric ratio
E_a	activation energy
EDG	electron-donating group
eq	equivalent(s)
Et	ethyl
E_T^N	"measure of solvent polarity"
g	gram
GC	gas chromatography
h	hour(s)
^1H	proton-1
HIV	human immunodeficiency virus
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
Hz	hertz
J	coupling constant value
K	equilibrium constant
kDa	kiloDalton
kJ	kiloJoules
LDA	lithium diisopropylamide
m	multiplet
M	molar
*m*BDPP	*meso*-2,4-bis(diphenylphosphino)pentane
Me	methyl
mg	milligram
MHz	megahertz
mL	millilitre
mol	mole
MS	mass spectrometry
MVK	methyl vinyl ketone
MW	microwave
NMDA	*N*-methyl d-aspartate
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance

o	ortho
OMs	mesylate
OAc	acetate
OTf	triflate
OTs	tosylate
Ph	phenyl
pKa	logarithmic measure of the acid dissociation constant
ppm	parts per million
Pr	propyl
^{i}Pr	isopropyl
q	quartet
quant.	quantitative
RNA	ribonucleic acid
rt	room temperature
s	singlet
S/C	substrate to catalyst ratio
t	triplet
TBAA	tetra-n-butylammonium acetate
TBAB	tetra-n-butylammonium bromide
Tedicyp	*cis*,*cis*,*cis*-1,2,3,4-Tetrakis(diphenylphosphinomethyl) cyclopentane
TEMPO	2,2,6,6-tetramethyl-piperidin-1-oxyl
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin Layer Chromatography
TMS	tetramethylsilane
TOF	turnover frequency
tol	tolyl
TON	turnover number
TsOH	toluenesulfonic acid

Chapter 1
Introduction

1.1 Catalysis

Catalysis is one of the most fundamental processes in nature. Without it, life itself would not exist as the vast majority of biologically relevant chemical processes rely on catalysis of some description. One theory on the origin of life relies on a predecessor of RNA becoming a catalyst for its own replication.[1,2] The importance of catalysis is indisputable, it is all around us, part of our everyday lives and, indeed, vital to our very existence.

A catalyst can be described as a component of a chemical reaction that actively participates in the reaction whilst not being consumed, allowing it to be used in substoichiometric (or catalytic) quantities. A true catalyst returns to its original state after a reaction ready to begin another cycle. The role of the catalyst is to lower the activation energy and hence increase the rate of reaction. Figure 1.01 shows how a reaction of **A** to produce **B** has a lower activation energy in the presence of a catalyst ($E_{a(Cat.)}$) than the same reaction in the absence of a catalyst ($E_{a(Uncat.)}$).

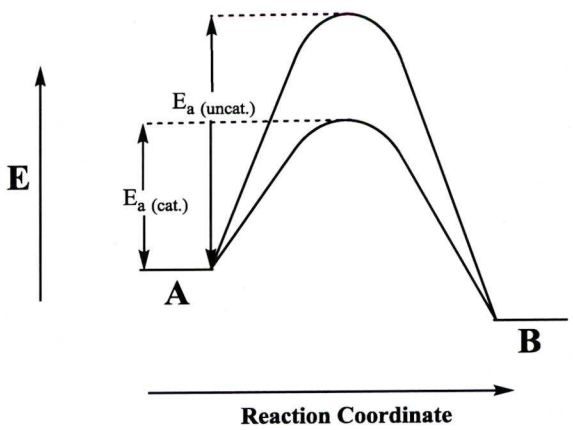
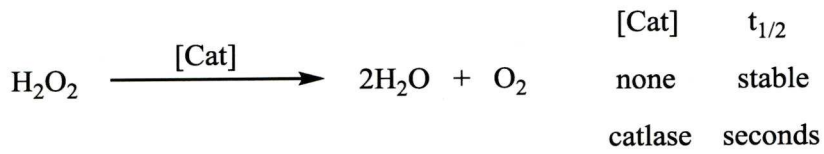


Figure 1.01 Difference in activation energy between catalysed and uncatalysed reactions

The difference in rate between catalysed/uncatalysed reactions can be on a scale of many orders of magnitude. For example, hydrogen peroxide is a relatively stable molecule, being stable enough to store at room temperature for long periods of time. However, if a catalyst in the form of the enzyme (catalase) is introduced, rapid decomposition occurs to water and oxygen (Scheme 1.01).[3]



Scheme 1.01. Catalysed and uncatalysed decomposition of hydrogen peroxide

The difference can be so great, in fact, for many transformations there is essentially no reaction without the addition of a catalyst. In addition to the increases in rate offered by catalysts, there are also the high levels of stereo-, chemo-, regio- and diastereoselectivity that can be achieved when a suitable catalyst is employed. For these reasons, the study and development of catalysis is of great interest to many researchers in a broad range of scientific disciplines. Energy sources,[4-6] pharmaceuticals,[7-10] fine chemicals,[11-15] petrochemicals,[16-19] automotive engineering[20-25] and food production[26-28] are just a few examples of areas that could benefit from an improved understanding and application of catalysis.

A great many types of catalyst exist; they range in size and complexity from a simple proton to elaborate metal complexes through to enzymes with molecular masses measured in kDa. The main classes would be considered as bio- (enzymes), molecular, transition metal and organo-catalysts. Also, depending on the state of the catalyst they can be further divided into heterogeneous and homogeneous.

As this thesis is concerned primarily with homogeneous transition metal catalysis the focus of this introduction will be on examples of this type. However, it is important at this point to further look at enzymes as they provide a great source of inspiration to those studying catalysis. The reason for this being that enzymes provide some of the fastest and most selective reactions known, all at mild temperatures and pressures in an aqueous environment. Carbonic anhydrase, the fastest known enzyme exhibits TOF's up to ca. 3 x 10^9 h^{-1}.[29,30] Palytoxin (Figure 1.02), with 73 asymmetric centres, 7 stereocontrolled C=C double bonds and numerous oxygen heterocycles, presented one of the most challenging total syntheses completed to date.[31] Given that palytoxin is a natural product it can be seen that nature, with her plethora of enzymes, can build amazingly complex molecules with relative ease. Of particular relevance is that many enzymes contain metal ions at their active site. These so-called metalloenzymes can be viewed as a reactive centre (metal ion) surrounded by a complex ligand system comprising a three dimensionally folded peptide chain. The well-defined tertiary and quaternary structures of proteins are the basis of the substrate specificity and reactive selectivity.

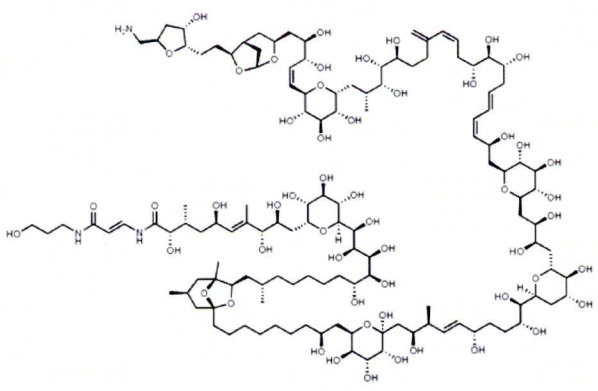


Figure 1.02. Structure of palytoxin

Given the features described above, it is not surprising that much work is directed towards mimicking the reactions of enzymes by incorporating their features into catalyst design.[32-36] Examples where the choice of metals, donor atoms/structure of ligands, cofactors and additives is inspired by enzymes are plentiful.[37-42] It does seem, however, as chemists we will always be playing catch up with nature and should continue to seek out the lessons we can learn in order to create faster, more selective catalysts.

1.2 Homogeneous transition metal catalysis

Transition metals have provided us with innumerable catalysts. From increasing the rate and selectivity of well-established reactions to the invention of brand-new ones, but what is it that makes transition metals such good catalysts? Although not exclusive to transition metals, some features of their chemistry are particularly prominent for these elements.

- *d-orbitals*- The outer most orbitals or valance shell of a transition metal is made up, by definition, of partially filled d-orbitals. The five d-orbitals shown in Figure 1.03 allow acceptance as well as donation of electrons to and from a substrate. This ability is vital for many organometallic processes found in transition metal catalysis.

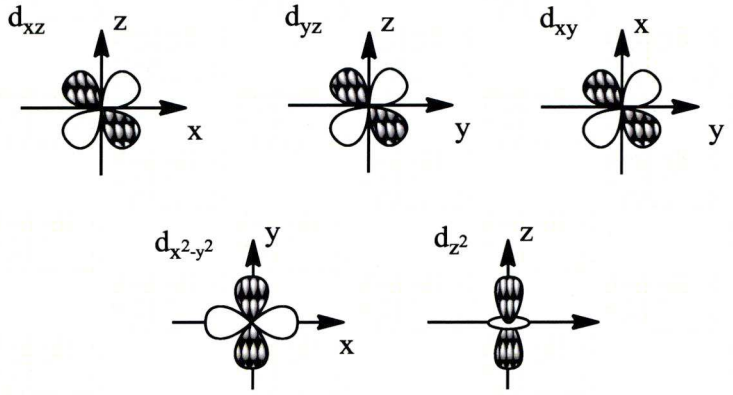


Figure 1.03. Representative diagram of the five d-orbitals

- *Variable oxidation state-* Catalytic cycles often involve steps where a change in oxidation state on the metal is necessary. Transition metals display the most diverse range of oxidation states in the periodic table. For example, stable complexes of vanadium in +2, +3, +4, +5 oxidation states can easily be prepared and switched-between in solution.[43] The stability of these ions and the low energy barriers between them are favourable characteristics for catalysis and quite typical of transition metals.

- *Complex formation-* By attaching ligands to a transition metal we are able to make complexes. By varying the ligands, metals and oxidation state an almost limitless number of complexes can be synthesised. The ligands encountered in modern coordination chemistry show unimaginable diversity. They serve many purposes including altering the electronic properties of the metal centre, stabilising unusual oxidation states, changing the steric environment and even find use in medical applications. For example, iron has well known chemistry in its II and III oxidation states. Less well known, outside of biological systems, are discrete complexes containing Fe(IV) and only in 1997 the synthesis of an Fe(V) complex was achieved outside of

polynuclear oxide chemistry (Figure 1.04).[44] Heavy metal poisoning, a rare but nonetheless serious condition can be successfully treated with chelation therapy by administering a ligand for the metal responsible and thus facilitating clearance from the body.[45-47] Succimer (Figure 1.04) is a ligand for lead that has been used to successfully treat patients with potentially fatal lead poisoning. Asymmetric transition metal catalysis owes its very existence to the ability of the metals to form complexes with chiral ligands.[48-50]

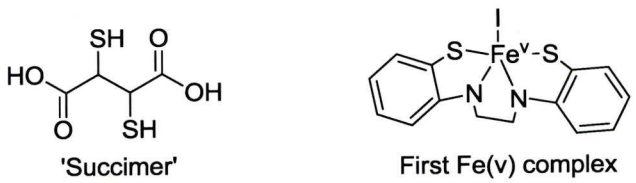


Figure 1.04 Ligands for high oxidation state stabilisation and medical applications

Given these features it is not surprising that almost every conceivable type of reaction has a transition-metal catalyst associated with it. Figure 1.05 shows some of the reactions that can be realised by homogeneous transition metal catalysis. Many of these reactions, although possible without catalysis, are faster, more selective, more economical and 'greener' than their uncatalysed counterparts.

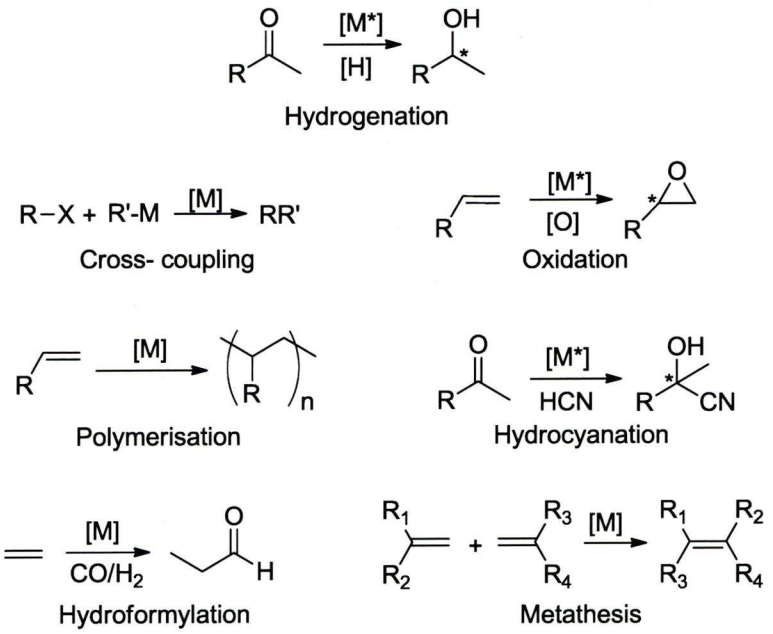


Figure 1.05. Homogeneous transition metal catalysed reactions

From an industrial point of view, homogeneous transition metal catalysts lagged behind their heterogeneous counterparts.[51] Until the late 1950's most industrially relevant reactions could be performed with solid catalysts. The easy recovery, re-use and operational simplicity make heterogeneous catalysis easier for large-scale application. The first industrial example of homogeneous catalysis was hydroformylation or the 'OXO' process. The reaction was discovered (1938) and developed by Otto Roelen, a man widely regarded as the forefather of industrial homogeneous catalysis.[52] Today it is still one of the largest commodity chemical processes with production of multi-million tonnes/year.[53] The attraction of homogeneous catalysis lies in the selectivity it can offer in reactions where there is a choice of products. The birth of organometallic chemistry with the discovery of ferrocene led to an explosion of research in the area that was paralleled by new homogeneous catalysts.[54] The production of highly active and selective catalysts was made possible by surrounding the metal with a suitable ligand. The industrial value

grew from ca. $100m in 1950 to >$23bn in 1985.[55] Another more recent trend that has helped the growth of homogeneous catalysis is the growth of the speciality and fine chemical industries.[8-10,14,15,27] Fuelled by an ever increasing demand for new pharmaceuticals, many companies are moving into the production of small volume, high value products. Many of these products are chiral or have some sort of selectivity involved in their synthesis, selectivity that can only be offered by homogeneous catalysis.

1.3 Palladium

Palladium (Pd) is element number 46 in the periodic table and resides in group 10 along with Ni and Pt. It is in the d-block or transition metals and can further be grouped into the platinum group or 'noble' metals.[56] The term 'noble' refers to the resilience of the metals to corrosion and oxidation and not to their reactivity. The metals in this group (Pd, Pt, Rh, Os, Ru, Ir) have a rich and diverse chemistry and their compounds make some of the best known catalysts. Unsurprisingly, this has led to transition metal catalysts using these metals being the subject of several Nobel prizes. Discovered in 1803 by William Hyde Wollaston, palladium is named after an asteroid 'Pallas' that was discovered around the same time. The techniques for the extraction and separation of palladium and other platinum group metals developed by Hyde are regarded as the foundation of the metallurgy of these elements.[57] Apart from use in catalysis, palladium metal is used for jewellery and electronics. The latter is one reason companies will buy old electronic devices. Recovery of the precious metals, including palladium, can be a profitable venture. The high prices paid for palladium reflect its rarity; very low yields of around 7 g per ton of ore are achieved

in the extraction process. A financial burden for many researchers is that for many reactions the best choice of metal tends to be the most expensive!

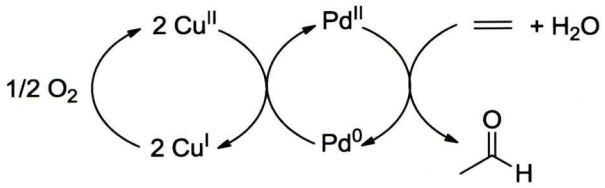
Some of the fundamental features of palladium chemistry may help explain why it is such a useful metal in catalysis. As well as those outlined in section 1.2, palladium has some additional advantages over the other metals in group 10. Complexes of palladium, when compared to Ni and Pt have moderate stability. Due to their respective sizes Ni complexes tend to be less stable and Pt more stable than analogous palladium counterparts. This appears to give palladium complexes a level of reactivity that is useful for catalysis.[56] An example of the stability of Pt complexes can be seen in Zeise's salt $[\{(\eta^2\text{-}C_2H_4)PtCl_2\}_2]$, one of the first organometallic compounds reported. This ethene coordinated crystalline complex is air and moisture stable at room temperature.[58] Palladium chemistry is dominated by Pd(II) and Pd(0) due to the high stability of complexes in these oxidation states. The low energy 'shuttle' between Pd(II)/Pd(0) means that many two-electron processes, often components of catalytic reactions, readily take place for palladium. Conversely, Ni is more prone to form Ni(0)/Ni(I) couples and so radical processes are more likely. This can lead to side products or lower selectivity in reactions where Ni is used in place of Pd. Pt has a very stable +4 oxidation state and so predominantly forms d^6-octahedral complexes, limiting its catalytic utility. Compared to the alkali and early transition metals, palladium is much more electronegative (Pauli = 2.2). As a consequence Pd-C bonds in organopalladium compounds are relatively non-polar. Thus, Pd catalysis is tolerant of functional groups such as carbonyls that other organometallics such as Grignard reagents would readily react with.

Organopalladium compounds can, therefore, be considered as complimentary to other organometallics.[56]

1.4 Homogeneous palladium catalysis

There are two commodity chemical processes that use homogeneous palladium catalysis in industry-

1. The 'Wacker' oxidation- Palladium has been known to oxidise ethylene to acetaldehyde in a stoichiometric process since Phillips reported the reaction in 1894.[59] Only in 1960, with the discovery of the 'Wacker' oxidation (Scheme 1.02) did this valuable transformation become industrially viable.[43] Catalysis was achieved by using $CuCl_2$ to oxidise the Pd(0) back to Pd(II). The resulting Cu(I) can then be readily be converted back to Cu(II) by O_2.



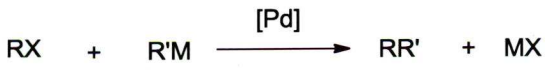
Scheme 1.02. The 'Wacker' oxidation

2. Shell polyketone synthesis[60]- It was 36 years from the discovery of the Wacker process until another homogeneous palladium catalyst made it onto the large scale industrial stage. Shell introduced a palladium-bisphosphine catalyst for the terpolymerisation of ethylene, CO and propylene to produce aliphatic polyketones. The original plant was built with a capacity of ca. 20 000 tonnes $year^{-1}$.

Palladium and cross-coupling reactions

If only looking at bulk chemicals, palladium appears underrepresented in an industrial sense. However, when looking to the fine or speciality chemical industries it has a much greater presence.[61-63] The last fifteen years in particular has seen the use of homogeneous palladium catalysis increase rapidly. This is mainly due to the plethora of cross-coupling reactions mediated by palladium.[64-67] Cross-coupling reactions, many catalysed by palladium, are now invaluable in organic synthesis and a summary of the most common types are shown in Table 1.1. In general, an aryl/vinyl/alkyl halide/triflate is coupled with an organometallic coupling partner to form a new C-C bond and eliminate a metal salt. Most of these reactions now have protocols that show excellent functional group tolerance and can be carried out at high S/C ratios at or below room temperature. There are also C-heteroatom bond forming processes such as the Buchwald-Hartwig amination that have made it to the industrial scale.[68]

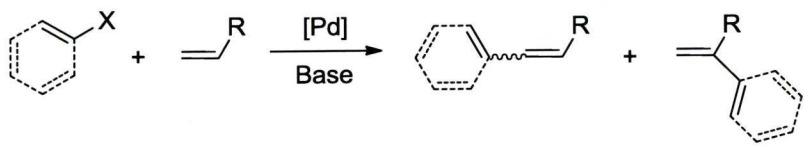
Table 1.1. Pd-catalysed cross-coupling reactions



Reaction	M	Reference
Suzuki	B	69,70
Stille	Sn	71,72
Kumada	Mg	73
Negishi	Zn	74
Hiyama	Si	75
Sonogashira	Cu	76,77

1.5 The Heck reaction

Following work on the transmetallation of organomercury compounds in the late 60's, [78-84] the Heck reaction was discovered independently and simultaneously by R.F. Heck[85] and T. Mizoroki.[86] Generally described as '*a reaction of an aryl/vinyl halide/triflate with an alkene in the presence of a base and a palladium catalyst*' (Scheme 1.03) It is now one of the most widely used C-C bond forming reactions in organic chemistry. The initial reports were followed by a series of papers by Heck where he demonstrated the potential of the chemistry to become what it is today.[87-90] The vast quantities of work produced since that discovery means no simple description can do justice to the rich and diverse nature of Heck chemistry. The list of aryl, vinyl,[91] and even alkylating[92] agents is growing all the time and it would seem that almost every solvent and base has, at some stage, been applied to the reaction.



Scheme 1.03. General scheme for Heck reactions

A large and ever increasing volume of literature (Figure 1.06) on the subject means that the Heck reaction has been reviewed on numerous occasions.[91,93-101] The level of fundamental research carried out has led to a greater understanding of the reaction and hence paved the way for more applications of the Heck reaction in total syntheses and fine chemical production.[7,8,15]

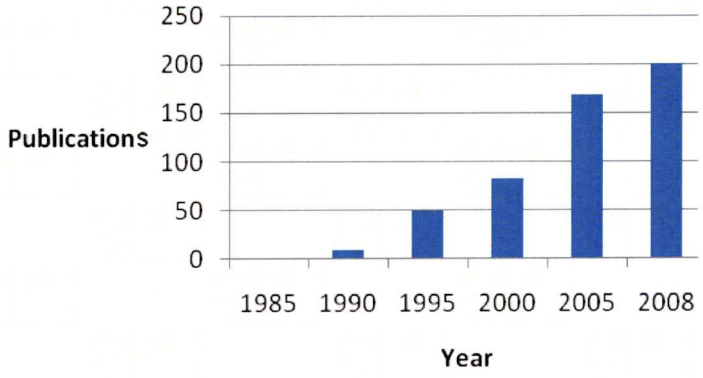


Figure 1.06. Number of publications vs. year for articles containing 'Heck' in the title (Web of Science)

Milestones in Heck Chemistry

Since its discovery, many developments have been made in Heck chemistry. There are, however, a few that stand out as particularly significant.

- Heck/Mizoroki 1971/2- Independant reports of a palladium-catalysed vinylation of aryl/vinyl halides emerged.[85,86]

- Spencer 1983/4- Two papers in this period realised the true potential of phosphine ligands to stabilise a palladium catalyst in polar solvents with a suitable base.[102,103] Ligands such as PPh_3 and P(*o*-tol)$_3$ allowed catalyst loadings as low as 0.0005 mol% and TON up to 134,000 to be achieved. Activated aryl chlorides were also able to react with the new catalyst system.

- Jeffery 1984- The use of additives such as NBu_4Cl in the Heck reaction is now referred to as the Jeffery conditions.[104] Quaternary ammonium salts provide advantages in a wide range of systems, probably due to the fact they can play many different roles.[104-109] They can be liquid-liquid or solid-liquid phase transfer agents, promoters of oxidative addition (halides), stabilizers of underligated or nanoparticulate palladium and ion exchange agents, all of

which are beneficial to the Heck reation. Specific examples will be discussed later.

- Herrmann/Beller 1995- The Herrmann-Beller palladacycle, derived from $Pd(OAc)_2$ and $P(o\text{-}tol)_3$ was found to be an excellent catalyst for the Heck reaction.[110,111] The preformed catalyst was found to be superior to the in situ generated complex. Although Spencer apparently unwittingly used the complex in his work of the early eighties,[102] noting $P(o\text{-}tol)_3$ was superior to PPh_3, it was not until Herrmann and Beller characterised and developed it as a preformed catalyst was the true potential of palladacycles realised. TON of up to 200 000 were achieved at catalyst loadings of 0.0005 mol %. This can be improved further still by the use of suitable additives. The catalyst was found to be applicable to a range of aryl bromides and an activated aryl chloride. The air, moisture and temperature stability of these complexes are particularly advantageous. Considerable work has gone into developing palladacycle catalysts and discovering their mode of action.[94,112-122]

- Herrmann 1995- The introduction of *N*-heterocyclic carbenes was another step forward in homogeneous transition metal catalysis, including the Heck reaction.[123] These new ligands showed remarkable coordination properties. Electronically they are similar to phosphine ligands in that they are excellent σ-donors but poor π-acceptors. They exhibit high thermal stability and are not generally air or moisture sensitive.[113] These properties make them very useful catalysts in the Heck reaction where they can be used at temperatures >140 °C. Phosphines are not generally able to operate under such harsh

conditions as they undergo well known decomposition pathways such as P-C bond cleavage.[124] The initial report used Pd loadings down to 10^{-4} mol%.

- Fu 2001- The Pd-P(^{t}Bu)$_3$/Cy_2NMe system introduced by Fu allowed the Heck reaction to be carried out under unprecedentedly mild conditions.[125] Aryl bromides and activated aryl chlorides reacted with a variety of olefins at room temperature. Unactivated aryl chlorides could also be coupled in a more general fashion than before. There were very few reports of reactions of this type previous to this report.

Further to the work above, interesting developments in Heck chemistry came with a somewhat surprising discovery linking the work of Jeffery and Herrmann/Beller. de Vries noted in 2003 that the 'ligand free' Heck reaction could proceed at extremely low or 'homeopathic' Palladium loadings without deactivation.[126] At these low loadings (0.01-0.1 mol %) the TOFs were actually greater than at higher loadings. An observation that, at first glance, seems counter-intuitive. It was noted that, at higher loadings, after an initial period of high TOF, rapid formation of palladium black was accompanied by loss of catalytic activity. It was suggested that the active catalytic species in these reactions is actually monomeric palladium and that an equilibrium exists between the active palladium, soluble palladium clusters and inactive palladium black. At the lower loadings this equilibrium is shifted more in favour of the monomeric palladium and the result is a higher catalytic activity and increased catalyst lifetime. It was also noted that the kinetic profile of the ligand free system and the Herrmann-Beller palladacycle were similar, an indication that the active species is the same in both cases. The palladacycle acts as a reservoir of monomeric palladium and the ligand serves to

prevent the aggregation to inactive clusters by stabilising the resting state of the palladium. The take home message from this work is that, in catalysis, less can indeed be more. One has to wonder how many examples where Heck chemistry has failed in syntheses could have benefited from these observations. There are, however, many examples where Heck chemistry has played a key role in total synthesis. Some prominent examples are outlined below.

Heck reactions in total synthesis

Intermolecular, intramolecular and asymmetric variants of the Heck reaction have all found a place in total syntheses. Some examples of compounds produced utilising the chemistry are shown in Figure 1.07. Estrone, a tetracyclic steroidal compound was synthesised enantioselectively by Tietze et al. using an intramolecular/intermolecular double Heck reaction.[127] (-)-Quadrigemine C[128] is a plant extract that shows analgesic and antibacterial properties. It was synthesised via a double asymmetric Heck reaction of an aryl triflate using a Pd-(Tol)-Binap catalyst. Taxol is an antitumor agent that is still in clinical use today. The total synthesis was achieved by employing an intramolecular Heck vinylation as a key bond forming step employing $Pd(PPh_3)$ as a catalyst.[129]

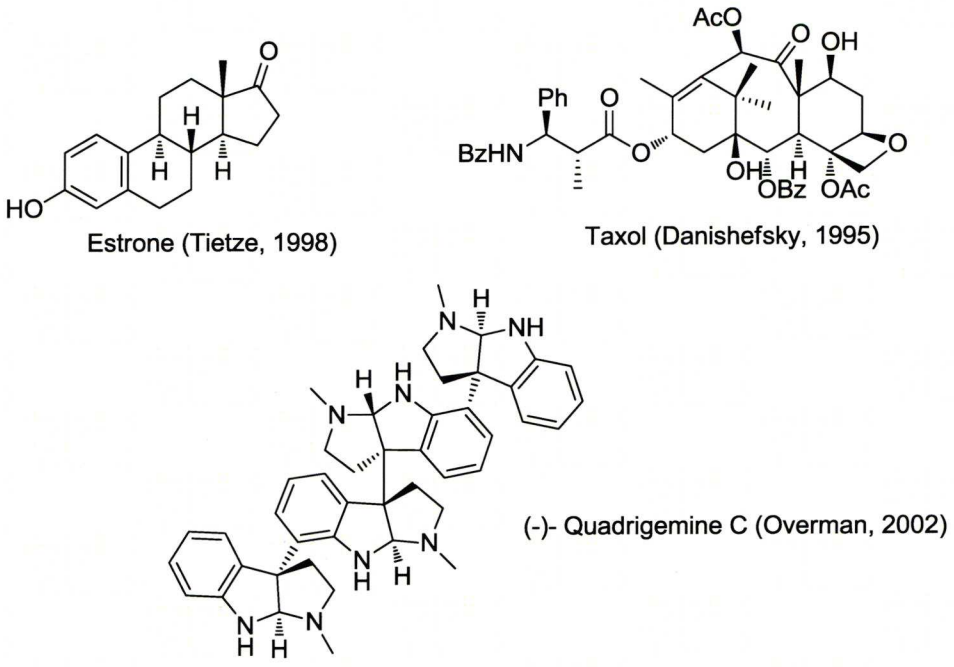
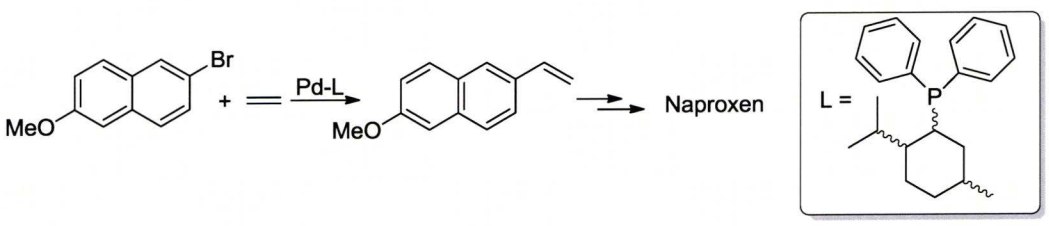


Figure 1.07. Total syntheses using Heck reactions as key steps

Industrial synthesis of pharmaceutical agents

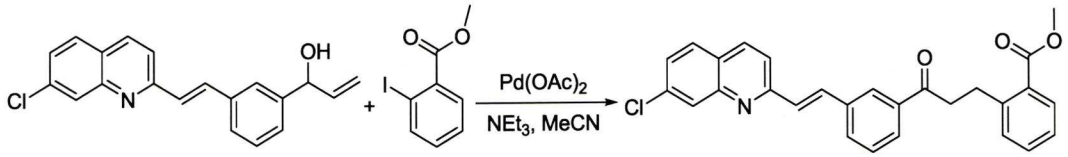
Naproxen, a non-steroidal anti-inflammatory drug, was produced on an industrial scale using the Heck reaction of 2-bromo-6-methoxynapthalene with ethylene (Scheme 1.04).[63] A palladium catalyst with an unusual neomenthyldiphenylphosphine ligand is employed for the reaction. Similar processes were also reported for related compounds using the Hermann-Beller palladacycle.



Scheme 1.04. Heck reaction in the industrial synthesis of naproxen

Montelukast sodium is an anti asthma drug used to treat children with the disease. A key transformation of the industrial synthesis was a Heck reaction of

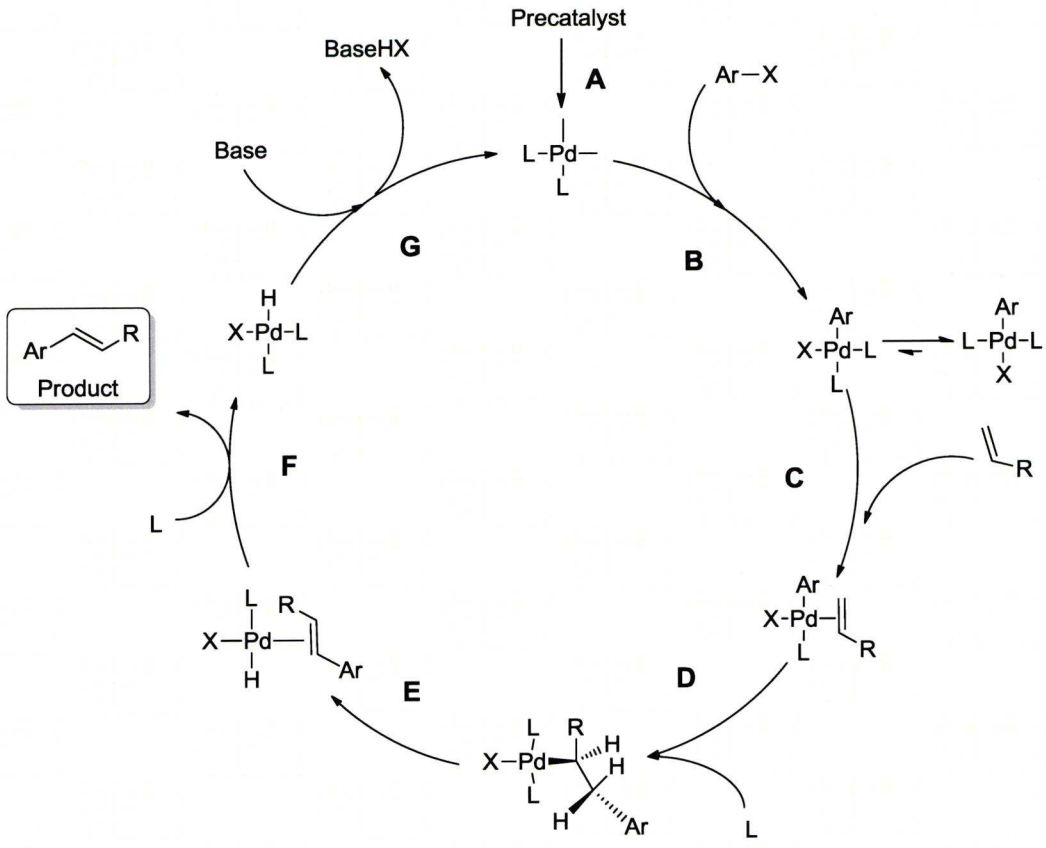
methyl-2-iodobenzoate with an intermediate allylic alcohol (Scheme 1.05). A simple catalytic system of $Pd(OAc)_2$ and NEt_3 in DMF achieved the C-C bond formation and isomerisation led to the desired ketone, an advanced intermediate in the synthesis.[63]



Scheme 1.05. Heck reaction in the industrial synthesis of montelukast sodium

1.6 Heck reaction mechanism

A textbook version of the generally accepted catalytic cycle for Heck reactions is shown in Scheme 1.06. Although immensely simplified, this representation is sufficient for basic understanding of the requirements of a Heck reaction.[100] In reality each step is a subject in its own right with numerous possibilities, the path taken depending on many factors and varying with what might seem to be trivial changes to the conditions, substrates etc.[91] Even with the wealth of knowledge gained through painstaking investigation, we are far from fully comprehending the entire picture and must continue to probe the mechanism so that more efficient, selective and convenient catalysts can be designed. After the catalyst activation in step **A** the actual catalytic cycle is made up of 5 fundamental organometallic steps. Oxidative addition **B**, olefin coordination **C**, migratory insertion **D**, β-hydride elimination **E** and finally reductive elimination **F** completes the cycle and regenerates the active palladium catalyst.



Scheme 1.06. The Heck catalytic cycle

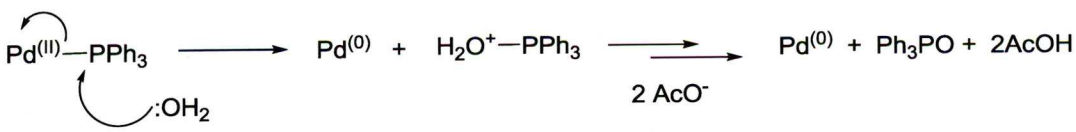
Preactivation step (**A**)

The metal precursors and ligands or, in fact, preformed metal complexes added to reactions, are in most cases not the active catalysts. These 'precatalysts' must undergo some form of transformation to a form where they are suitable to enter the catalytic cycle. This transformation is termed 'preactivation' and almost all Heck reaction catalysts must go through this step. The active catalytic species in the Heck reaction may be a dicoordinate Pd(0) species (Pd-L_2). The term dicoordinate is used with the exclusion of transient ligands such a solvent molecules and refers only to strongly bound ligands such as phosphines, amines, carbenes etc. The two most

common preactivation processes are reduction of Pd(II) to Pd(0) and the equilibrium processes that lead to the correctly ligated Pd species.

Reduction of Pd(0) to Pd (II)

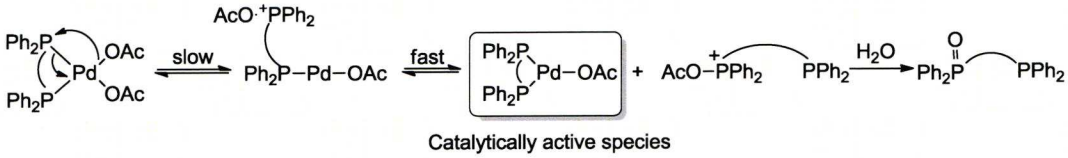
Amatore and Jutand have extensively investigated this step and identified several key factors that determine the final palladium species generated. They have identified potential active catalytic species in several detailed reports.[130-137] Because of their ubiquitous nature, it is probably most appropriate to address the mode by which phosphines can reduce Pd(II) to Pd(0). A coordinated phosphine is itself attacked at the central phosphorus atom by a nucleophile. In the process two electrons are transferred to palladium, reducing it to the catalytically active zero oxidation state. Water is the most likely candidate to play the role of the nucleophile and the driving force for the reaction is formation of the extremely stable phosphine oxide after decomposition of the initially formed phosphonium salt. Scheme 1.07 shows a common example of $Pd(OAc)_2$ being reduced by PPh_3 and H_2O though the process occurs with many $Pd^{(0)}$ precursors, ligands and nucleophiles.[136]



Scheme 1.07. Reduction of Pd(II) to Pd(0) by PPh_3 and H_2O

In addition to this general mechanism there is the more specifically relevant example provided by Amatore and co-workers.[137] In a $Pd(OAc)_2$/bisphosphine system where two equivalents of the bidentate ligand are used, one equivalent of the bisphosphine monoxide is formed. The palladium is reduced by the chelating

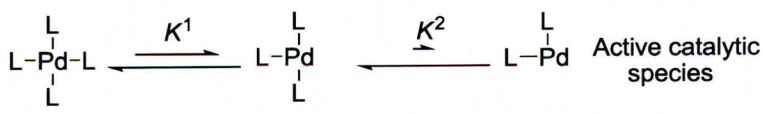
phosphine via an inner-sphere mechanism involving a coordinated acetate ion. The phosphine/phosphonium ligand undergoes a substitution reaction with the remaining bisphosphine and generates the bisphosphine/acetate/palladium complex thought to be the catalytically active species.



Scheme 1.08. Catalytically active species generation from $Pd(OAc)_2$ and bisphosphines

Generation of dicoordinate Pd through pre-equilibrium

There is somewhat of a paradox that exists when considering how to increase the chances of generating the required dicoordinate palladium (Pd-L_2). Scheme 1.09 shows the equilibrium involved to reach the active species from a typical four coordinate palladium precursor. Usually, $K^1 >> K^2$ so [Pd-L_2] is very small.[136,138] On one hand intuition would lead us to reduce the amount of ligand so that only two (in the monodentate case) are available, driving the equilibrium to the right. Indeed this does lead to an increased [Pd-L_2] but at high enough concentrations a fast and irreversible decomposition to palladium aggregates or 'palladium black' occurs. To combat this problem increasing the amount of ligand would be a logical solution. Unfortunately this would drive the equilibrium in Scheme 1.09 too far to the left and render [PdL_2] too low for effective catalysis. It is, therefore, necessary to optimise the amount of ligand for each new reaction or use strongly binding ligands such as carbenes. This said, for monodentate phosphine ligands 3-4 equivalents will usually suffice.



Scheme 1.09. Pre-equilibrium leading to the catalytically active Pd-L_2

Oxidative addition **(B)**

The first step to be truly within the catalytic cycle is oxidative addition. This is the fundamental process by which an underligated transition-metal complex is added across a C-X (X = Cl, Br, I, OTf, OMs ...) bond, in the process increasing its oxidation number by 2 i.e. Pd(0) to Pd(II). Oxidative addition is sensitive to, amongst other factors, the strength of the C-X bond and the electronic properties of the metal atom. Of course, steric factors in the substrates and ligands, solvent, temperature and pressure can all exert an effect on the rate of the process but we will concentrate on the aforementioned.[131,139-146] As determined by Jutand and Amatore, the order of reactivity for the most commonly used substrates in oxidative addition follows the general trend I>>OTf>Br>>Cl.[130] Unfortunately this trend is also true for the cost and availability of the substrates so a compromise between economy and reactivity must be found. As the metal atom involved is oxidized, increased electron density will increase the rate of oxidative addition. One might be tempted into thinking that simply increasing the electron-donating capability of the ligands would lead to an increased rate of oxidative addition and hence, in cases where it is the rate limiting step, increase the overall reaction rate. This is fundamentally true and electron-rich ligands are superior to others for oxidative addition. However, for the reasons outlined above there is a limit to the benefit that can be gained by increasing the electron-donating capability of the ligands. If the ligands are bound too strongly the metal centre K_2 may become too small for an effective reaction to take place.

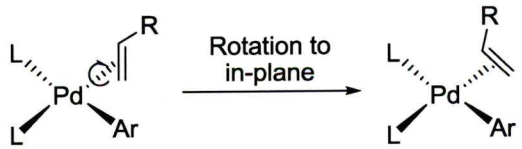
Olefin coordination **(C)**

In order for the C-C bond forming step of migratory insertion to occur, the olefinic coupling partner must be coordinated to the palladium. This requires a

vacant coordination site on palladium and therefore dissociation of one ligand. The nature of the ligand that dissociates can have consequences for the regioselectivity of the reaction (*vide infra).* Many descriptions of the olefin coordination would lead a reader to believe it was a dissociative process. In reality it is likely that an associative mechanism is in operation and the four-coordinate η^2-vinyl species is reached via a five-coordinate palladium intermediate.[147]

Migratory Insertion **(D)**

Migratory insertion is the C-C bond forming step of the catalytic cycle. It is the regioselectivity and, in asymmetric variants, the stereoselectivity determining process. For electron-rich olefins this is particularly relevant and is discussed in detail later. An important feature of the migratory insertion is the requirement that the C=C bond of the olefin must be in the palladium square plane. For this to occur, the olefin must rotate through 90° from its initial perpendicular coordination mode. It has been shown that the barrier to rotation could be a rate limiting process (*vide infra*).

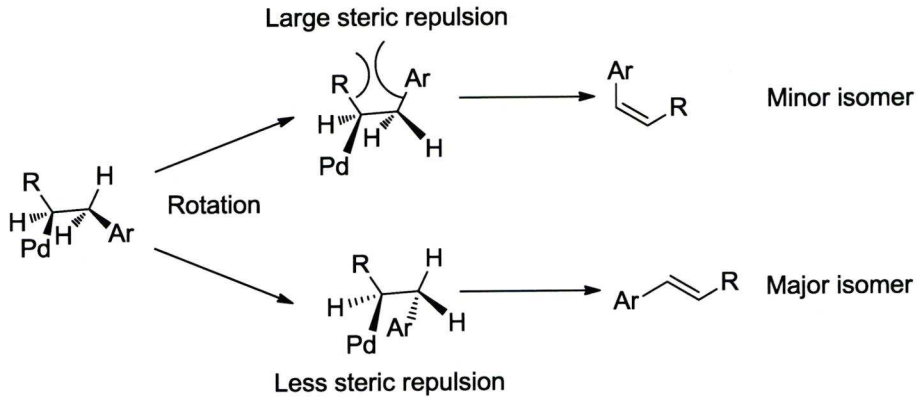


Scheme 1.10. Rotation of coordinated alkene into the Pd square plane

β-Hydride elimination **(E)**

β-Hydride elimination is the step in which the product is released from the catalytic cycle. It is also the step in which the stereochemistry of the product is decided. Immediately following migratory insertion, Pd and the aryl/vinyl group are in a *syn* relationship (Scheme 1.11). As the hydride elimination requires a *syn*

relationship of Pd and H an internal rotation must take place. For monosubstituted alkenes undergoing aryl/vinylation at the β position there is a choice of hydride. The hydride eliminated is predominantly the one that reduces the steric interactions between the R group and the aryl/vinyl group. Unless R is very small this leads to high *E* selectivity. For reactions of monosubstituted alkenes where α selectivity occurs to produce 1,1'-disubstituted products, there is no choice of hydride and no stereochemical issues. The hydride elimination results in the product alkene being coordinated to the palladium in an η^2 mode and displacement of one other ligand.



Scheme 1.11. Internal bond rotation and β-Hydride elimination

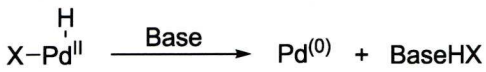
Product dissociation **(F)**

The ligand that dissociated in step **E** now comes in and, through a substitution reaction, releases the product from the palladium. The *cis* complex formed by this reaction is the correct geometry for the final step of the catalytic cycle, reductive elimination of HX.

Reductive Elimination **(G)**

The final stage of the catalytic cycle is the reductive elimination of HX from the palladium complex (Scheme 1.12). Assisted by an appropriate choice of base the

palladium is reduced from Pd(II) to Pd(0). The catalytically active species is regenerated and can now enter a fresh catalytic cycle. The choice of base can have dramatic effects on the Heck reaction and can be the difference between complete failure and a highly successful reaction.

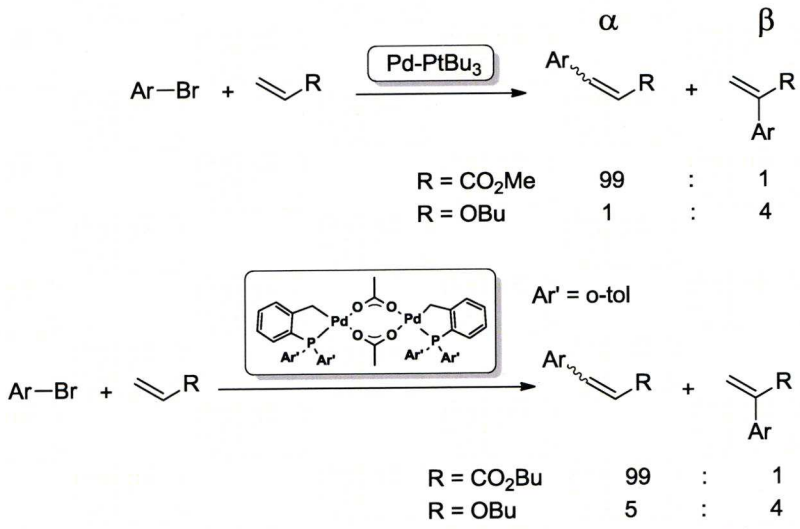


Scheme 1.12. Reductive elimination of HX from XPdH

1.7 Electron-rich vs. electron-deficient olefins

The Heck reaction can be divided into two distinct groups, depending on the nature of the olefinic partner. Reactions of electron-deficient olefins such as acrylates and styrenes are well-studied and excellent catalysts exist for their arylation, vinylation and in some cases alkylation. TOFs up to 300 000 and TONs of 5.7×10^6 h^{-1} can be achieved, with Pd-loadings that are below the permitted level of Pd for an API.[93] Some complexes can catalyse the reaction at room temperature whilst maintaining acceptable reaction rates and catalyst loadings.[148-152] The reactions are highly regioselective with substitution being achieved almost exclusively at the β position of the double bond.[91,98,153]

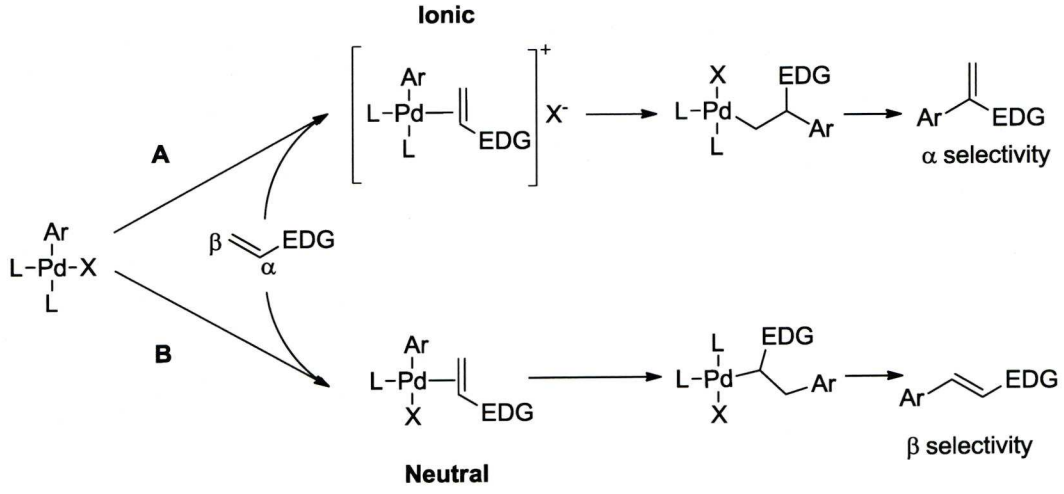
The same cannot be said, however, for electron-rich olefins such as enol ethers, enamines and unsaturated alcohols. They are much less studied, suffer from lower reactivity and, perhaps most importantly, their reactions are not regioselective. This lack of regioselectivity is exemplified by two well known catalysts that are highly successful for reactions of electron-deficient olefins, namely Fu's Pd-P^tBu_3[148] and the Hermann-Beller palladacycle.[110] Scheme 1.13 shows how the regioselectivity drops when moving from electron-deficient to electron-rich olefins.



Scheme 1.13. Regioselectivity of Heck reactions with a palladacycle and Fu's Pd-P(^{t}Bu$_3$)

Mechanistic rationale

Now well established is the fact that the Heck reaction can proceed *via* two different mechanisms.[96,98,154] The two mechanisms differ only in the nature of the ligand that dissociates to leave a vacant coordination site for the incoming olefin, (Scheme 1.14). The neutral pathway (**B**) occurs when a neutral ligand, usually a phosphine, leaves the coordination sphere of Pd, the ionic pathway (**A**) occurs when an anionic ligand (Cl^-, Br^-, I^-, ^-OTf) dissociates. The pioneering work of Cabri in the early 1990's led to the suggestion that the two different pathways are responsible for the two different products obtained in some reactions of electron-rich olefins.[155-157] The neutral and ionic pathways give rise to β and α substitution respectively.



Scheme 1.14. The ionic and neutral pathways of the Heck reaction

Theoretical work from the groups of Svensson and Brown has confirmed an electronic basis for the selectivity.[158-160] It was believed, as recently as 2000, that steric factors were more important than electronic.[91] Theoretical studies have also revealed, for certain substrates, that the regioselectivity can be independent of the pathway.[158] The credibility of theoretical work in this area is strengthened by its agreement with experiment. Brown and co-workers' paper on the prediction of regiochemistry in the Heck reaction conforms to the results obtained in experimental studies.[158]

This does raise the question of what the electronic effects are and why they have such a profound effect on the selectivity. Let us first consider the different classes of olefin under 'neutral' Heck conditions. Figure 1.08 shows how the regiochemical outcome of the reaction varies greatly depending on the group attached to the olefinic bond. For electron-deficient olefins such as acrylates, acrylonitrile, allylic alcohols and vinylogous amides, only β substitution products are obtained. Electron-withdrawing substituents activate the β carbon of the double

bond. This, combined with steric effects, leads to exclusive substitution at the β position, regardless of the pathway followed. Electron-donating substituents activate the α- carbon of the olefin and so would be expected to preferentially undergo substitution at this position. However, the polarisation of the double bond is not as strong as it is in the case of electron-deficient olefins. As a consequence, when the neutral pathway is followed, vinyl ethers, *N*-vinyl amides, vinyl acetates and other electron-rich olefins generate a mixture of products.

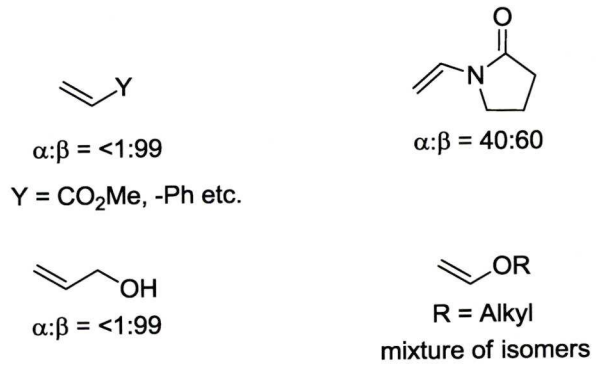


Figure 1.08. Regiochemical outcome with various olefins under 'neutral' Heck conditions

If we now consider the same substrates under 'ionic' Heck conditions the results are considerably different for electron-rich olefins. Electron-rich olefins are excellent σ-donors, this gives them a high affinity for the highly electrophilic Pd-centre generated upon dissociation of an ionic ligand.[161] This affinity explains why, under ionic conditions, electron-rich olefins are more reactive than their electron-deficient counterparts. Once coordinated, the polarisation of the C-C double bond is increased and the α-carbon is activated to a greater extent than in the neutral case. This is exaggerated further by the fact that they are poor acceptors of π-electrons. With the increased α-activation comes an increased tendency for migratory insertion to occur onto the α-position (Figure 1.09.).

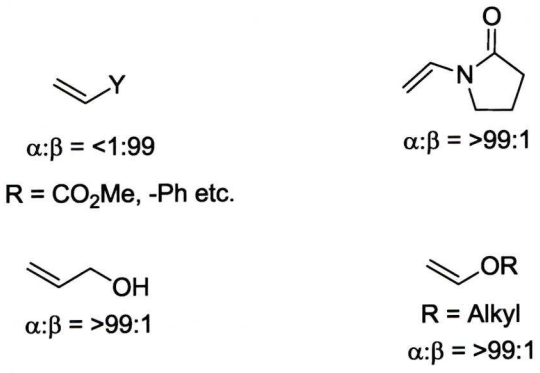


Figure 1.09. Regiochemical outcome with various olefins under 'ionic' Heck conditions

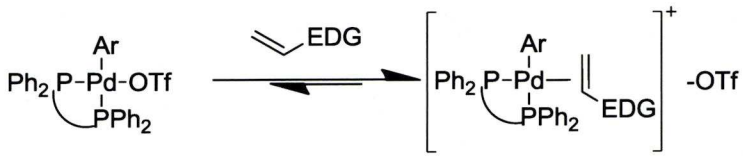
Practical procedures for promoting the ionic pathway

Both experimental and theoretical evidence suggest that the ionic pathway of the Heck reaction results in α-substitution in the Heck reaction of electron-rich olefins. It is, therefore, necessary to adjust conditions in order to promote this pathway to obtain regioselectivities that are synthetically useful. Several methods currently employed to achieve this are described below.

Use of labile counterions

The early work of Hallberg demonstrated that by using labile counterions (e.g. –OTf) the regioselectivity in the arylation of butyl vinyl ether was changed to be in favour of the α position (scheme 1.15).[162,163] These results agree with the need to generate a cationic palladium species prior to migratory insertion as a more facile dissociation of $^{-}$OTf compared to I^{-}, Br^{-} or Cl^{-} will drive the equilibrium to the right. There are, however, several problems with using triflates as aryl/vinylating agents. They are not generally commercially available, can be expensive and thermally labile.[162-165] This has inspired other groups to develop alternatives to triflates.

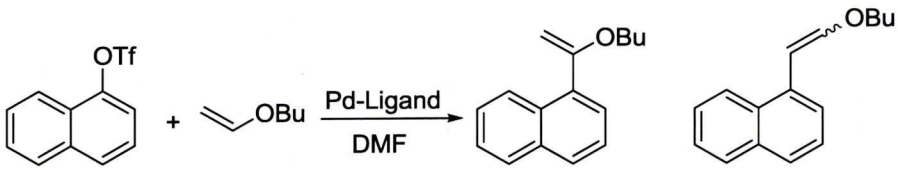
Mesylates (-OMs) and tosylates (-OTs) have both been utilized as effective replacements for the problematic triflates.[166]



Scheme 1.15. Formation of cationic palladium via dissociation of triflate

Bidentate Ligands

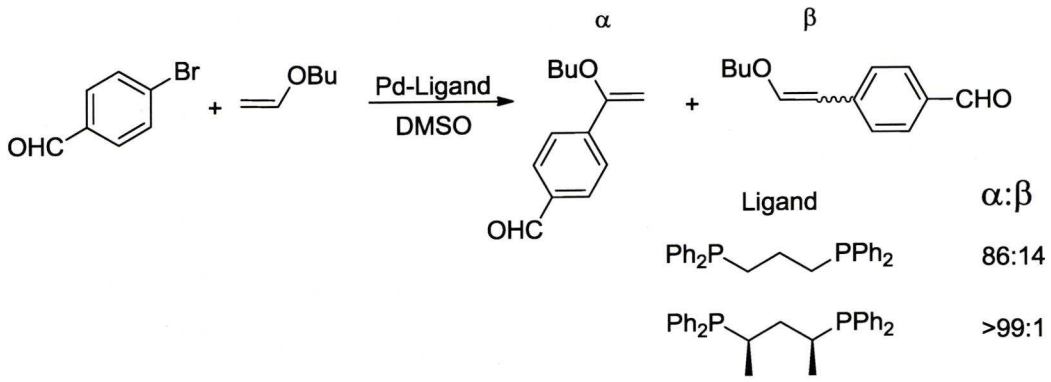
Following his original report in 1990[167] Cabri explicitly demonstrated the ability of bidentate ligands such as bis-1,3-(diphenylphosphino)propane (dppp) to direct the Heck reaction of electron-rich olefins such as butyl vinyl ether (BVE) in favour of α substitution.[96,155,161,167] Hence, in the arylation of BVE by 1-napthyl triflate the α:β ratio increased from *ca* 60:40 when no ligand or PPh_3 was used, to >99:1 when the chelating bisphosphine dppp was employed (scheme 1.16). Interestingly, in this example the regioselectivity is unaffected by a change in solvent and the regioselectivity remains at >99:1 in dioxane and toluene. Chelating bidentate phosphines are now chosen as a matter of routine when α selectivity is required.



Ligand	α	β
None	54	46
PPh_3	63	37
dppp	>99	1

Scheme 1.16. Ligand effects on regioselectivity of butyl vinyl ether arylation

Although dppp is the ligand of choice for the reactions under question, Xiao et al. have shown in experimental and theoretical studies that subtle differences in the ligands can have significant effect on the rate and regioselectivity of the reaction when using aryl halides. In common solvents the use of a Pd-dppp catalyst leads to a mixture of products. Hence, in the arylation of BVE by 4-bromobenzaldehyde an α:β ratio of 86:14 was obtained using Pd-dppp in DMSO. Switching to the structurally very similar *meso*-2,4-bis(diphenylphosphino)pentane (*m*BDPP) increased the ratio to >99:1 under similar conditions (Scheme 1.17).[168]



Scheme 1.17. DPPP vs. *m*BDPP for arylation of electron-rich olefins

Recently, the same group have shown that electron-withdrawing groups on the aryl rings of the ligands can accelerate the arylation of a variety of electron-rich olefins (Figure 1.10).[169] It was postulated that this is due to a lowering of the energy barrier to migratory insertion, the step widely believed to be rate limiting. DFT calculations revealed these ligands do indeed lower the insertion barrier and the conversion is correlated with the calculated activation energy. This lowering of the activation energy was tentatively attributed to easier rotation of the olefin to the required in-plane orientation and increased electrophilicity of the Pd-centre.

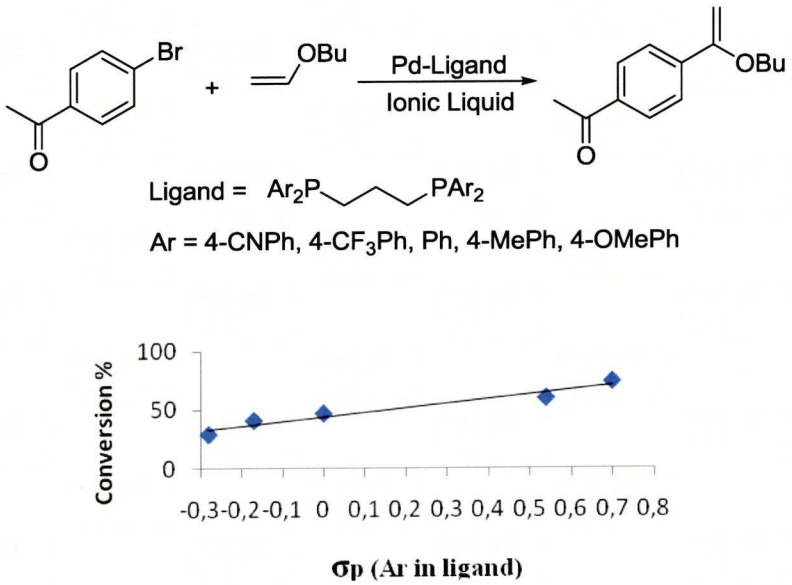


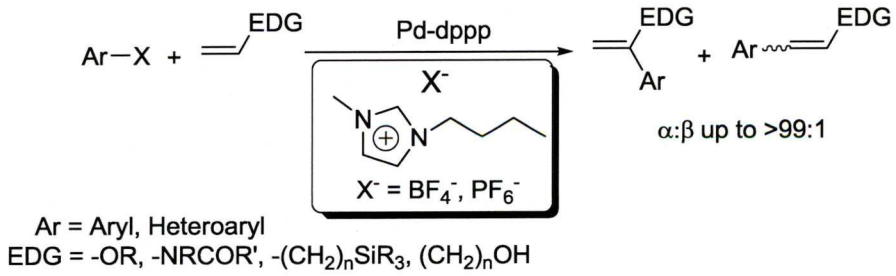
Figure 1.10. Conversion vs. electronic properties of dppp based ligands

Halide Scavengers

Another tactic used to promote the ionic pathway is the addition of halide scavengers to the reaction mixture. The addition of silver (I) and thallium (I) containing salts such as TlOAc to reactions where aryl halides were employed allowed for regioselectivities of >99:1 to be achieved.[170,171] This is presumably because the presence of these ions encourages dissociation of the halide ligand and hence generation of the required cationic Pd-species. There are, however, problems associated with the addition of such salts to these reactions. For the additives to be effective they must be used in at least stoichiometric quantities. Using large quantities of toxic thallium or expensive silver renders the use of these additives on a large scale implausible.

Ionic Liquids

Ionic liquids have received a lot of attention in recent years for a variety of applications.[172-178] Comprising entirely of ions these room temperature, molten salts can stabilise any ions or extremes of charge generated during the course of a reaction. For this reason it was suggested by Xiao that, if employed as solvents, the ionic environment could promote the ionic pathway and hence highly regioselective arylation of electron-rich olefins. This was indeed the case and ionic liquids such as [Bmim][BF_4] (scheme 1.18) afforded regioselectivities of up to >99:1 for the arylation of a variety of electron-rich olefins. Enol ethers, enamides, unsaturated silanes, and unsaturated alcohols could all be arylated with excellent regioselectivities in good to excellent isolated yields.[154,170,179-184] Worthy of special note is that activated aryl chlorides could, for the first time, be utilised for the arylation of electron-rich olefins, albeit at elevated temperature and in moderate yields.

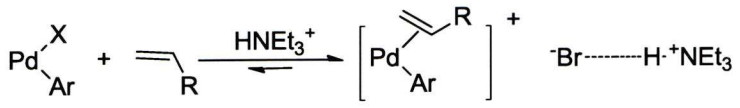


Scheme 1.18. Ionic liquids as solvents for Heck reactions of ionic liquids

H-Bond Donors

Xiao and co-workers also found that the addition of H-bond donating ammonium salts such as [$HNEt_3$][BF_4] and [H_2NiPr_2][BF_4] had a beneficial effect on the reaction under question in both conventional and ionic media.[182] In ionic liquids

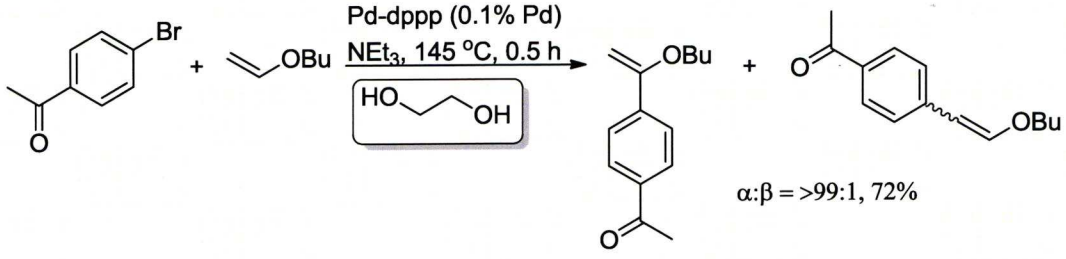
rate accelerations of up to 12 times were observed. For conventional solvents such as DMF, both the rate and selectivity were increased. In the presence of 1.5 eq $[HNEt_3][BF_4]$ almost exclusive α selectivity was obtained in the reaction of aryl bromides in DMF, previously only possible with the addition of Ag or Tl salts. The ammonium additives provide a cheaper and less toxic alternative to their metallic counterparts. It is suggested that the additives encourage dissociation of the bromide from the palladium by H-bonding interactions, thus promoting the ionic pathway (Scheme 1.16).



Scheme 1.19. Generation of cationic palladium promoted by H-bond donors

Alcohol solvents

Following on from the success of H-bond donating salts, the use of alcohol solvents such as ethylene glycol provided one of the best systems for the arylation of electron-rich olefins.[185] Given the success of added H-bond donors, the highly H-bonding environment provided by the alcohols would be expected to provide fast and regioselective reactions. Figure 1.20 shows how the arylation of the benchmark butyl vinyl ether can be carried out in ethylene glycol at S/C >1000 achieving full conversion in <0.5 h. As with the ammonium salt additives it is thought the H-bonding facilitates dissociation of bromide from Pd. This argument is strengthened by the correlation of the E_T^N values (a measure of H-bond capability) of 21 solvents and rate of the reaction.



Scheme 1.20. Regioselective Heck reaction in ethylene glycol

1.8 Aims of the thesis

The previous sections have hopefully gone some way to show how Heck chemistry has developed into a versatile and indispensable reaction in organic chemistry. We have seen how it has now become such a large subject area that one cannot simply study 'the Heck reaction'. The variety of chemistry contained under this umbrella term is plentiful and justice cannot be done to the immense diversity of Heck chemistry in one thesis. The frontiers are being pushed all the time and what was once thought impossible can now be achieved as a matter of routine.[91]

The Heck reaction of electron-rich olefins has come a long way since the days when these substrates were considered problematic. Pioneering work in the groups of Cabri, Hallberg, Larhed, Xiao and others has allowed the aryl/vinylation of electron-rich olefins to become selective and more facile. However, there still remains scope for further expansion into new areas. This thesis aims to explore relatively neglected or unexploited branches of the chemistry and build on the remarkable progress made in recent years. Particular attention will be paid to reactions of vinyl halides and tandem/one-pot procedures. Vinyl halides have received relatively little attention when compared to aryl halides so an investigation of these substrates reacting with electron rich olefins will be undertaken. If

differences between aryl/vinyl halides exist it may be possible to design catalytic systems dedicated to vinyl halides and improve the efficiency of these reactions. Recent work in this group has shown that alcohol solvents, particularly diols, are excellent for promoting highly regioselective and fast arylations of electron-rich olefins. It has also been observed that exchange between products of the Heck reaction and alcohol solvents can occur, incorporating the sovent into the product in the form of cyclic ketals. We hope to exploit these observations and develop cascade reactions for the formation of cyclic ketals utilising cheaper reagents than those employed in other related reactions. The regioselective Heck arylation of unsaturated alcohols is challenging and as such there are few methods that can successfully achieve this reaction. The final chapter of this thesis aims to develop a one-pot procedure whereby a regioselective internal Heck arylation is followed by intramolecular hydroalkoxlation leading to substituted oxygen heterocylcles.

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Chapter 2

Regioselective Heck Vinylation of Electron-Rich Olefins

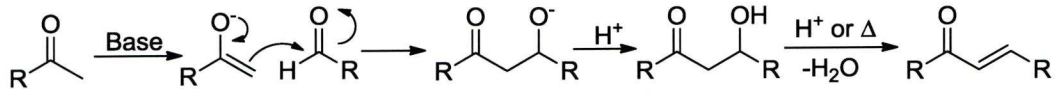
2.1 Introduction

α,β- Unsaturated ketone synthesis

The compounds produced by the reactions developed in this chapter are primarily α,β- unsaturated ketones. They are of interest to, amongst others, the pharmaceutical,[1-3] food[4] and cosmetic[5] industries as end products or precursors to desired compounds. Because of their far-reaching interest a great many methods exist for their preparation; some of the most popular are outlined below. In cases where appropriate the methods are exemplified by their application to the synthesis of (*E*)-4-phenylbut-3-en-2-one, a compound these reactions have in common with this work.

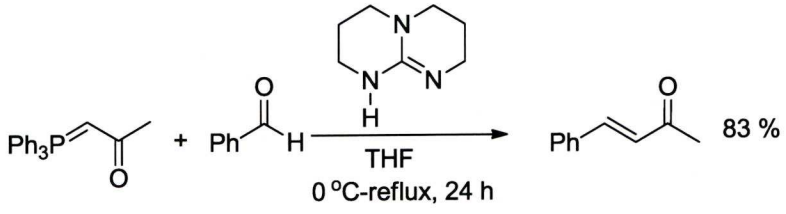
Possibly the most well-known method for the synthesis of α,β- unsaturated ketones is the aldol reaction. First reported by Wurtz in 1872,[6] it has now become one of the most widely used C-C bond forming reactions in organic chemistry.[7-10] Enolates generated from a carbonyl compound and a base are reacted with an aldehyde in the key bond forming step. The initially produced *β*-hydroxy ketone can dehydrate leading to formation to the C=C double bond and the desired enone. A typical example is shown in Scheme 2.01[11]. The reaction is wide ranging and versatile but is not without problems. In compounds where there are more than one set of enolisable protons, selectivity issues exist. A mixture of products can result and careful control of the reaction conditions is required to favour the desired

product. Generation of some enolates requires strong bases such as LDA, meaning low temperatures and reagents such as BuLi are necessary.



Scheme 2.01. The aldol reaction

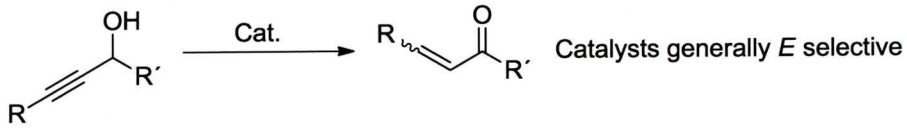
The Wittig reaction can also be utilised for α,β-unsaturated ketone synthesis.[12-14] Phosphorus ylides react with a carbonyl compounds forming a new C=C double bond and a phosphine oxide, the strength of the phosphorus oxygen bond being the driving force for the reaction. The stereoselectivity can be poor and products are often obtained as *E/Z* mixtures. However, conditions have been developed that allow *E*-selectivity in the production of unsaturated ketones. An example is shown in Scheme 2.02[14].



Scheme 2.02. The Wittig reaction for enone synthesis

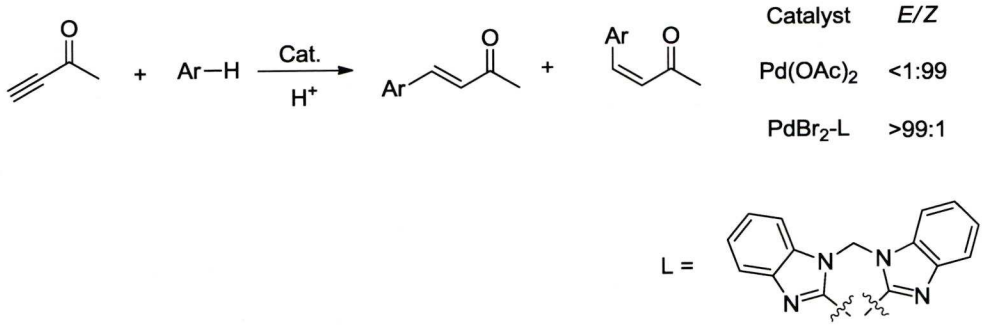
Propargylic alcohols are isomers of α,β-unsaturated ketones. Catalysts have been developed that can isomerise the alcohols to the corresponding ketones in what is known as the Meyer-Schuster rearrangement (Scheme 2.03).[15-19] The reactions involve oxidation of an alcohol to a ketone and reduction of an alkyne to an alkene. Metals including, but not limited to, Ru[20], Mo[21], Pd[16], Ir[22] and Au[23] have all been employed in the reaction. The mechanism is dependent on the catalyst and conditions but can generally be viewed as follows. The hydrogen is 'borrowed' from the starting

alcohol by the catalyst upon alcohol oxidation and delivered back upon reduction of the alkyne in an intramolecular process.[18] As the reaction is conducted in the absence of H_2 over-reduction to the alkane is not a problem. The complete atom economy of this reaction makes it particularly attractive. Homogeneous catalysts can produce enones with excellent *E/Z* selectivity, generally in favour of the *E* isomer.[17,18]



Scheme 2.03. Isomerisation of propargylic alcohols to enones

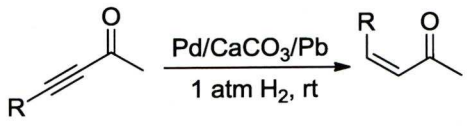
In recent years, the hydroarylation of ynones (sometimes referred to as the Fujiwara reaction) has become recognised as one of the most promising C-C bond forming reactions.[24,25] It involves the formal hydroarylation of an alkyne in the prescence of a metal catalyst. Interestingly, the first catalysts developed gave very high *Z* selectivity.[24] Very recently catalysts based on Pt and Pd have been reported that offer excellent *E* selectivity.[25] With the Pd catalyst shown in Scheme 2.04, (*E*)-4-phenylbut-3-en-2-one was produced in an 87 % yield after 5 h at 80 °C reaction with 0.1 % catalyst loading. As with the isomerisation of propargylic alcohols, atom economy is an attractive feature of this reaction.



Scheme 2.04. Hydroarylation of ynones

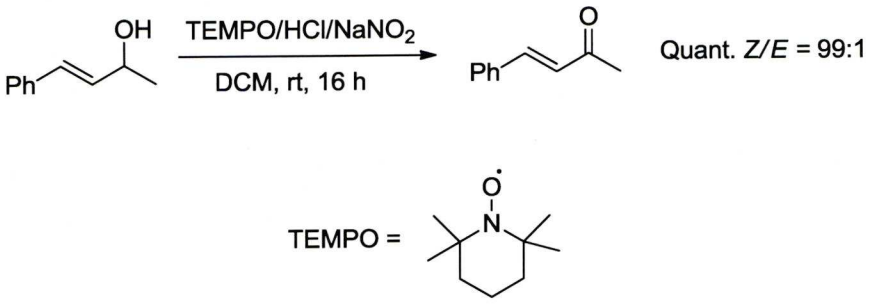
An Au based catalyst was developed by Zhang and co-workers for the reaction of propargylic acetates with electron rich arenes.[26] The reaction produces α,β- unsaturated ketones and has a good scope. The reaction conditions are mild and the yields for the compounds reported are good to excellent. For (*E*)-4-phenylbut-3-en-2-one, 2 mol% of the catalyst PPh_3AuNHC (*N*-Heterocyclic carbene) allowed for an 82% yield in 16 h at room temperature. The product was obtained with excellent *E* selectivity. The reaction has also been investigated by the group of Nolan.[27]

Another method for synthesis of enones is the semihydrogenation of appropriate alkynes (Scheme 2.05). In these reactions, avoiding over-reduction of the multiple bonds to a saturated system is the main challenge. A popular tactic for achieving this is to use a poisoned metal catalyst; the reduced activity prevents reduction of the newly formed alkene. Lindlar's catalyst, Pd on calcium carbonate poisoned with lead, is perhaps most widely used for this purpose. The reactions can be conducted under mild conditions, typically room temperature and atmospheric pressure of H_2. However, the procedure can be somewhat laborious and strict monitoring of hydrogen uptake is required.[28,29] As with other heterogeneous hydrogenation catalysts, the products are predominantly in the *Z* configuration.[30] Homogeneous catalysts have also been developed to selectively produce both *Z* and *E* alkenes. Elsevier developed a Pd-carbene catalyst for the transfer hydrogenation of alkynes using an HCO_2H/NEt_3 azeotrope.[31] A range of alkynes were successfully reduced and 4-phenylbut-3-en-2-one was obtained with a solvent dependant *E* stereoselectivity of < 93:7.



Scheme 2.05. Semihydrogenation of enones with Lindlar's catalyst.

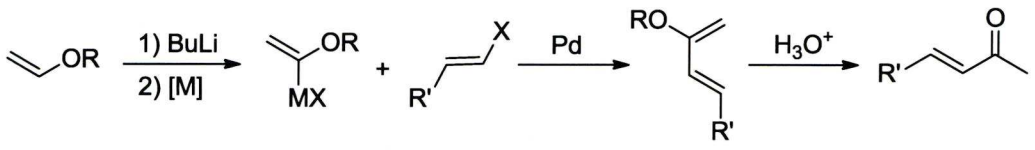
The oxidation of alcohols to ketones is one of the most fundamental processes in organic chemistry. Oxidation of secondary allylic alcohols yields α,β-unsaturated ketones. Pd,[32] Cu,[33] and Ru[34,35] catalysts can all achieve this oxidation with high efficiency. More recently, non-metal systems have been developed based on halide or acidic catalysts with oxygen as a terminal oxidant. Liang and co-workers introduced TEMPO/HCl/$NaNO_2$ as a mild, efficient catalytic system for the oxidation of a variety of alcohols to aldehydes and ketones, including enones, in air at ambient temperature (Scheme 2.06),[36]



Scheme 2.06. Oxidation of allylic alcohols to enones

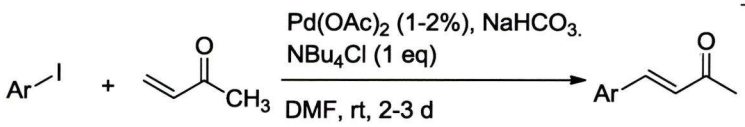
Cross-coupling reactions developed by Negishi[37] and others[38-40] are another method by which to obtain α,β-unsaturated ketones. A palladium catalyst promotes the coupling of vinyl halides/triflates with an organozinc[37], tin[38] or silicon[39] compound derived from electron-rich olefins. Lithiation of the olefin followed by transmetalation generates the olefinic coupling partner that then reacts with an arylpalladium species to initially produce a 1,3-diene. In the case of alkyl vinyl

ethers the 2-alkoxy 1,3-dienes can be hydrolysed by aqueous acid to the corresponding α,β-unsaturated ketones.



Scheme 2.07. Pd-catalysed coupling of vinyl halide/triflates with an organometallic enol ether

The Heck *arylation* of unsaturated alkyl vinyl ketones produces cinnamyl ketones. For example, in his seminal paper on the use of phase transfer agents such as NBu_4Cl as additives for the Heck reaction, Jeffery reported the arylation of methyl vinyl ketone (MVK) with several aryl iodides.[41] Although the reaction could be carried out at 25 °C and the yields were excellent (97-98%), long reaction times (2-3 days) were required for Pd loadings of 1-2 % (Scheme 2.08).

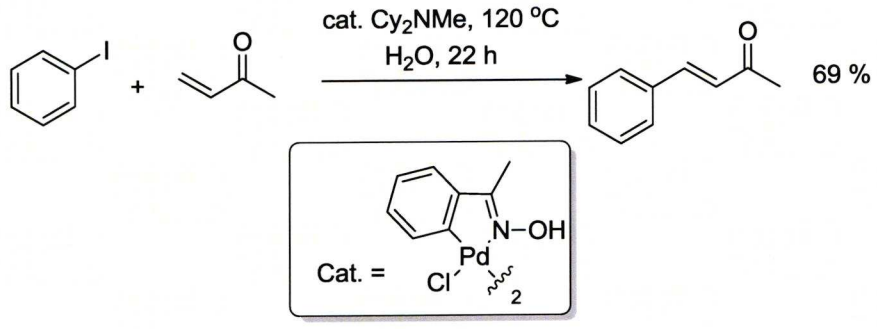


Ar	yield (%)
Ph	98
m-MeC_6H_4,	97
p-ClC_6H_4	98
p-$OMeC_6H_4$	97

Scheme 2.08. Jeffery conditions for the Heck arylation of MVK

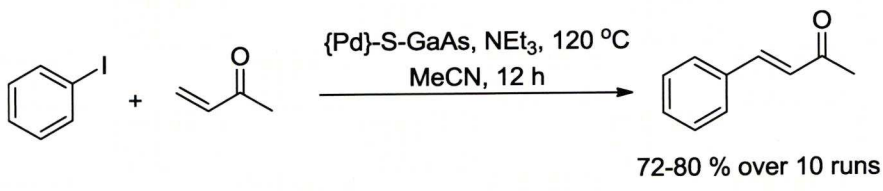
The Pd-complex in scheme 2.09 developed by Nájera was used for the mono- and diarylation of MVK in aqueous conditions.[42] With a Pd loading of 9×10^{-3} mol% and using Cy_2NMe as base, the Heck reaction of phenyl iodide and MVK in H_2O at 120 °C for 22 h gave (*E*)-4-phenylbut-3-en-2-one in 69% yield.[43] A supported version of this complex could also catalyse the reaction in aqueous conditions. An average

yield of 88 % over two runs at 0.01% Pd loading could be obtained in 7-8 h at reflux temperature.[44]



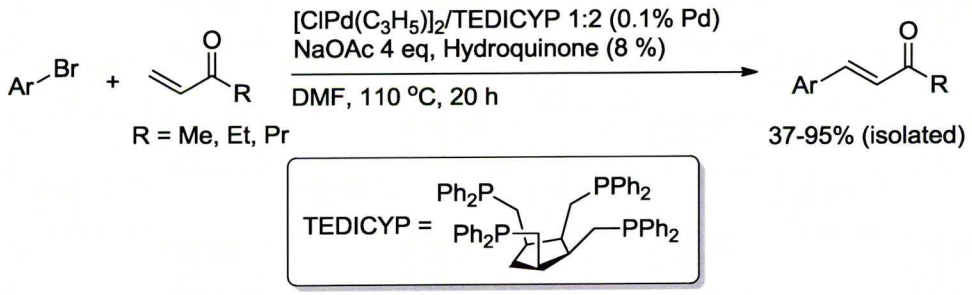
Scheme 2.09. Pd-oxime complex for the aqueous Heck arylation of MVK

Supported catalysts are attractive because the ease with which they can be recycled means they can be economically and environmentally more viable for large scale processes. Many examples of supported catalysts for the Heck reaction are available.[45-49] Nishida and co-workers developed a Pd-S-GaAs (Scheme 2.10) catalyst that successfully catalyses the Heck reaction between Ph-I and MVK.[50] With NEt_3 as base in MeCN at 100 °C, (*E*)-4-phenylbut-3-en-2-one was obtained in 76% yield. The catalyst could be recycled for ten times and with an optimised washing procedure, essentially no loss of catalytic activity was observed and Pd leaching was minimal. It is noted, however, that the yields obtained with MVK were significantly lower than those with methyl acrylate (97-100%, ten runs), a common feature when MVK is the olefin.



Scheme 2.10. Heck reaction of phenyl iodide and MVK with a supported Pd catalyst

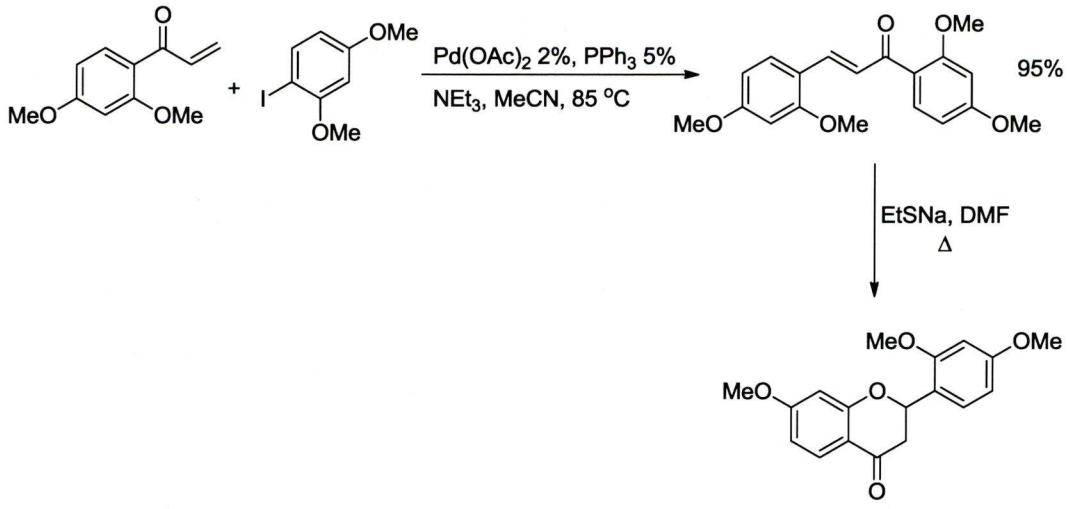
cis,cis,cis-1,2,3,4-Tetrakis(diphenylphosphinomethyl) cyclopentane or TEDICYP complexes of Pd (Scheme 2.11) were found by Santelli and co-workers to be a good general catalysts for the Heck arylation of enones with aryl bromides.[51,52] Aryl bromides had not been used in a general fashion for these reactions prior to the introduction of this ligand, an overwhelming majority of the literarure focussed on aryl iodides.[41-44,50,53-72] In DMF, a range of (*E*)-1-aryl alk-1-en-3-ones were produced in moderate to good yields with Pd loadings as low as 0.001 mol%. Reaction times were generally 20 h at 110 °C. Other more common ligands such as PPh_3 were found to be less effective for demanding substrates such as 9-bromoanthracene and did not allow catalyst loadings as low as those achieved with TEDICYP. Hydroquinone was added as a stabiliser for the vinyl ketones in 8 mol%. The author points out that commercially available MVK is stabilised with the same additive and yields and catalyst loadings were improved in its presence. It is, therefore, likely that the lower yields generally obtained with alkyl vinyl ketones are due to the instability of the alkene under the reaction conditions.



Scheme 2.11. TEDICYP as a ligand for the Pd-catalysed arylation of MVK with aryl bromides

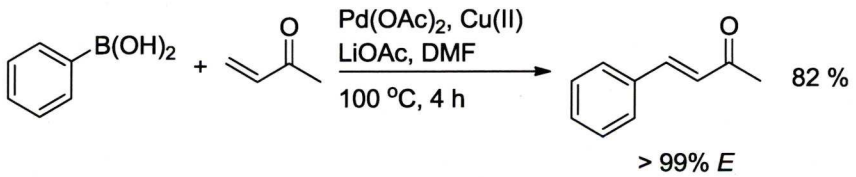
The Heck reaction on aryl vinyl ketones has also been developed and used in the preparation of chalcones and flavanoids, two important classes of naturally occurring compounds.[63] A Heck reaction of substituted arylvinyl ketones with aryl iodides was carried out under typical conditions to obtain the coupling product in

yields approaching quantitative. Subsequent steps converted the resulting chalcones into the desired flavanoids. An example is shown in Scheme 2.12.



Scheme 2.12. Heck reaction of aryl vinyl ketones for Chalcone and Flavanoid synthesis

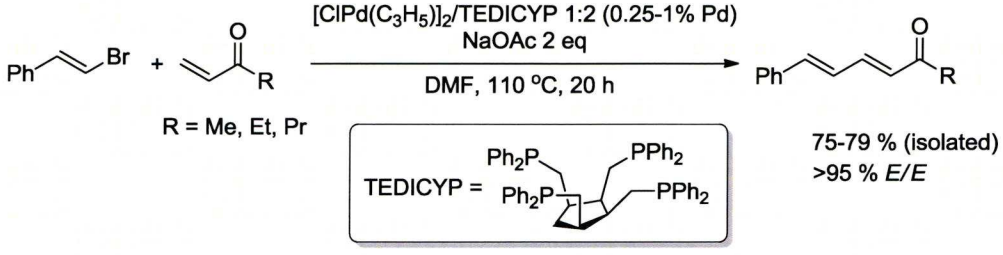
Apart from the conventional Heck coupling of aryl/vinyl halides, there is also the oxidative Heck reaction that utilises boronic acids as aryl/vinylating agents. Because the end of the Heck catalytic cycle releases Pd(0) and these reactions require Pd(II), either stoichiometric Pd must be used or catalytic Pd in conjunction with a stoichiometric oxidant. Cu(II) was used as an oxidant by Kosugi and co-workers for the Heck reaction of MVK with phenylboronic acid. A 4 h reaction in the presence of 5% Pd gave the cinnamyl ketone product in 82% yield with >99% stereoselectivity for the *E* alkene.[73] However, recent work from the Xiao group has shown that the oxidative Heck reaction can take place without external oxidants.[74]



Scheme 2.13. Oxidative Heck reaction to produce cinnamyl ketone

Heck reaction of vinyl halides and derivatives

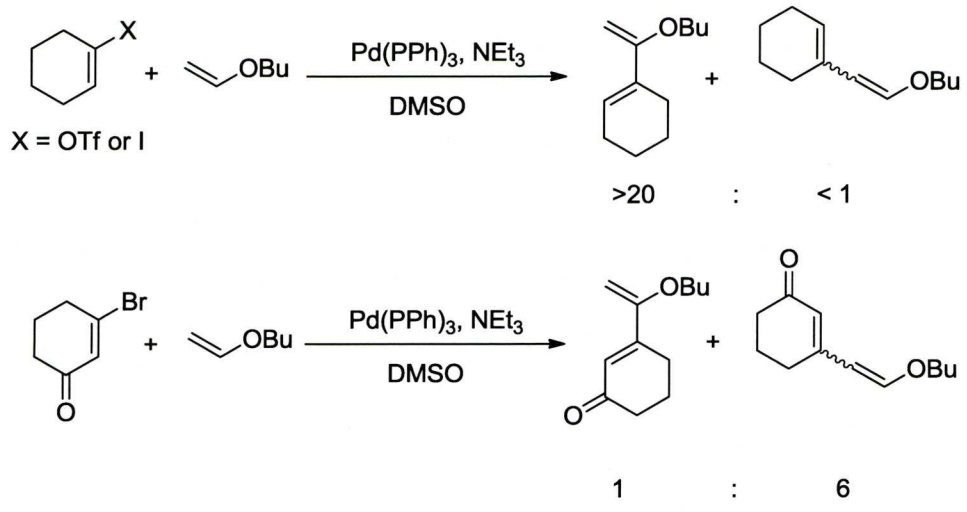
The Pd/TEDICYP catalyst developed by Santelli and co-workers was able to catalyse the reaction between β-bromostyrene and a range of electron-deficient olefins (Scheme 2.14).[75,76] These included a few enones and catalyst loadings of 0.25-1 mol% allowed for the conjugated dieneones to be obtained in 75-78% isolated yields. These two papers represent rare examples of reports focusing on the Heck vinylation of olefins.



Scheme 2.14. Pd-TEDICYP catalyst for the vinylation of olefins with vinyl bromides

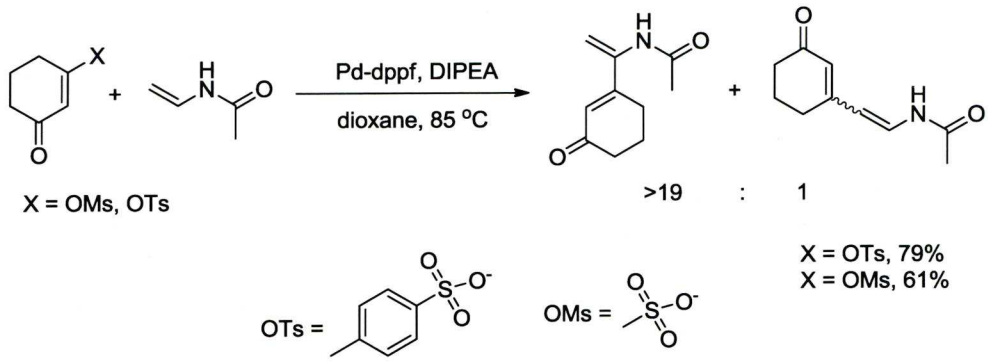
Whilst generally treated as analogous to arylation, the vinylation of electron-rich olefins is relatively unexplored. Vinylations are usually found as additional examples within papers primarily concerned with arylation and similar conditions are used when applying them to the Heck reaction. For vinylation of electron-rich olefins, only a handful of papers exist.

Early work by Hallberg *et al* showed that high selectivity for branched products could be achieved in the reaction of vinyl iodides and triflates with 3 mol% $Pd(PPh_3)_4$ in DMSO (Scheme 2.15).[77] High α:β ratios (>20:1) were obtained for electron-rich vinyl triflates and iodides. However, when the substrate was changed to an electron-deficient vinyl bromide, the selectivity was reversed and *β* substitution predominated.



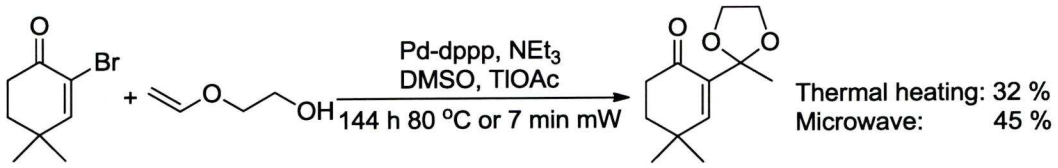
Scheme 2.15. Heck vinylations of an electron-rich olefin catalysed by $Pd(PPh_3)_4$

The realisation by Cabri that bisphosphine ligands increase the α-selectivity of arylation reactions was taken on board by those studying the vinylations.[78-82] These ligands have been routinely used since then to obtain the required regioisomer, DPPP and DPPF being the most common choice. As mentioned in Chapter one, the use of triflates can be considered somewhat problematic. Skrydstrup and co-workers have addressed some of the issues associated with triflates by employing mesylates and tosylates as vinylating agents (Scheme 2.16).[83] A range of electron-rich olefins reacted including enol ethers and enamides. They are cheaper and less thermally labile than triflates, offering a significant advantage. Mesylates, however, produce lower yields of the desired products compared to tosylates. For example, the vinyl tosylate shown in Scheme 2.16 gave 79% isolated yield when reacted with N-vinyl acetamide compared to 61% for the corresponding mesylate under similar conditions. The regioselectivity was equally high in both cases (> 19:1).



Scheme 2.16. Heck vinylation of electron-rich olefins with mesylates and tosylates

Hallberg and co-workers took advantage of microwave irradiation to drastically increase the rate of reaction between vinyl halides/triflates and electron-rich olefins.[84] Reaction times were reduced to minutes rather than hours and in some cases gave higher yields. Where the regioselectivity was < 99:1 thermal heating was always superior to microwave. Thus, in the reaction of the vinyl bromide from Scheme 2.17 with BVE the regioselectivity (α/β) dropped from 98/2 to 80/20 upon switching from conventional to microwave heating. They also demonstrated that hydroxyalkyl vinyl ethers could be used to obtain unsaturated cyclic ketals once they had been vinylated. The reactions with vinyl bromides provided isolated yields of 10-67% in 20-144 h. 2-Alkoxy 1,3-dienes or cyclic ketals were obtained from the vinyl triflates in better yields (> 89%) in 20 h with thermal heating. It should be noted that from this paper, it appears that halide scavengers such as TlOAc are necessary to obtain good regioselectivity.



Scheme 2.17. Cyclic ketals from a vinyl bromide with mW or conventional heating

All of the above examples were carried out with vinyl iodides, bromides, triflates, mesylates or tosylates. There is, however, another class of vinylating agents that only three reports have addressed, the vinyl chlorides. Fu's Pd-P(^{t}Bu)$_3$/Cy$_2$NMe allowed, for the first time, the coupling of an unactivated vinyl chloride with an olefin.[85] A yield of 66% was achived after 46 h at 110 °C with a 3% Pd loading. Another example employed the somewhat unusual tropanoids as vinylating agents with a Pd(PPh$_3$)$_4$ catalyst.[86] High pressure was used to promote the coupling of a vinyl chloride with styrene in the presence of a Pd(OAc)$_2$/PPh$_3$/NEt$_3$ system.[87] The yields were modest (42%), reaction times long (3 d) and pressures of 10 kbar (!) were required for successful reaction.

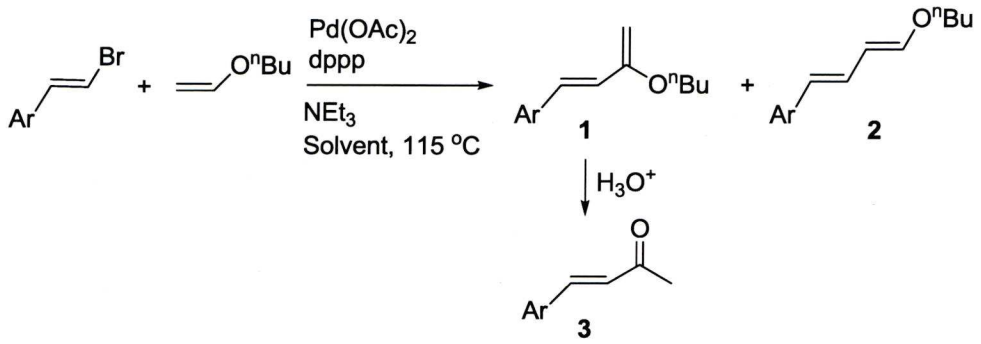
Because vinyl halides have not enjoyed the same attention as aryl halides and related compounds we decided to investigate their reactions with electron-rich olefins in detail. Our aim was to see if the treatment of vinyl halides under the same conditions as aryl halides was indeed the best course of action. Are vinyl halides indeed analogous to aryl halides? If not, can a better catalyst be found for the vinylation of electron-rich olefins?

2.2 Results and discussion

As a starting point for our study on the vinylation of electron-rich olefins, we applied the arylation conditions developed within this group to the reaction of *p*-methoxy-*β*-bromostyrene with n-butyl vinyl ether (BVE).[88-94] Table 2.01 shows the results obtained with 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF$_4$]) as solvent. In contrast to the analogous arylation, the Pd-dppp catalyzed vinylation was sluggish in the ionic liquid, and addition of hydrogen bond-donating salts did not have an accelerating effect on the rate (Entries 1 and 2). Entries 3 and 4 show that

this is also true in the molecular solvent DMSO and no significant effect on the rate was observed upon addition of the ammonium salt.

Table 2.01. Vinylation of electron-rich olefin in ionic liquid vs DMSO[a]



Entry	Solvent	Additive [b]	t (h)	Conversion (%)	Selectivity[c]
1	[bmim][BF_4]	None	20	40	>99:1
2	[bmim][BF_4]	[$HNEt_3$][BF_4]	20	33	>99:1
3	DMSO	None	0.5	61	>99:1
4	DMSO	[$HNEt_3$][BF_4]	0.5	66	>99:1

[a] Reaction conditions: *p*-methoxy-*β*-bromostyrene (1 mmol), BVE (3 mmol), $Pd(OAc)_2$ (3 mol%), dppp (6 mol%), NEt_3 (3 mmol) in 2 mL solvent at 115 °C; bmim = 1-^{n}butyl-3-methylimidazolium; conversion measured by ^{1}H NMR. [b] 1.5 mmol added where appropriate. [c] Molar ratio of **1:2**; >99:1 assigned when **2** was not detected by ^{1}H NMR and GC.

The reaction proceeded very well in DMSO, affording over 60% conversion in just 0.5 h (entry 3). And significantly, the reaction exhibited remarkable selectivity for the products resulting from α substitution, as no linear product could be detected by ^{1}H NMR or GC-MS. Again, the addition of hydrogen bond-donating salts had negligible effect on the rate (entry 4). A solvent screen revealed that DMSO was superior to the other common Heck solvents tested and that changing the trialkylamine base from NEt_3 did not have any beneficial effect on the rate (Table 2.02).

Table 2.02. Screening of solvents and bases for the Heck vinylation of BVE[a]

Entry	Solvent	Base	Conversion (%)
1	DMSO	NEt_3	61
2	DMF	NEt_3	32
3	dioxane	NEt_3	15
4	toluene	NEt_3	18
5	DMSO	NBu_3	55
6	DMSO	HN^iPr_2	50
7	DMSO	$MeNCy_2$	58

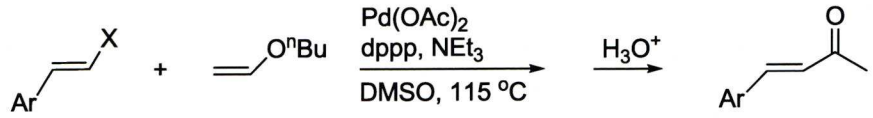
[a] Reaction conditions: *p*-methoxy-*β*-bromostyrene (1 mmol), BVE (3 mmol), $Pd(OAc)_2$ (3 mol%), dppp (6 mol%), Base (3 mmol) in 2 mL solvent at 115 °C; conversion measured by ^1H NMR.

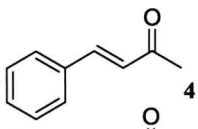
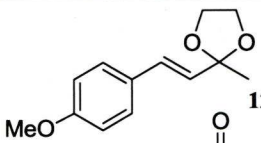
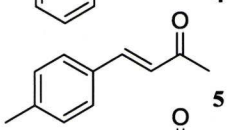
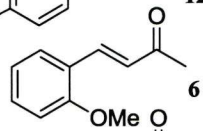
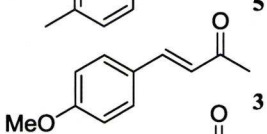
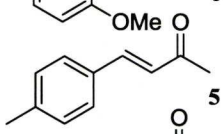
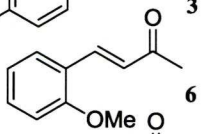
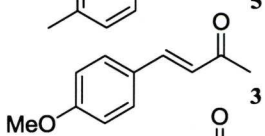
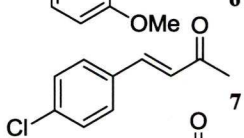
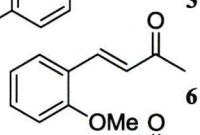
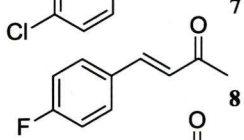
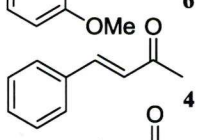
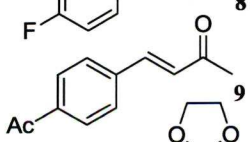
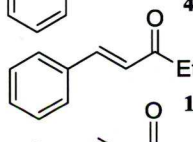
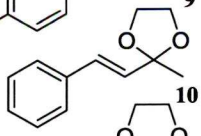
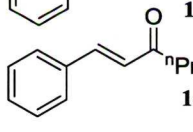
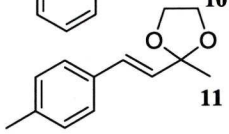
These results show that the α-vinylation of electron-rich olefins catalysed by Pd-dppp can work in a common, molecular solvent with no need for any additives. By applying the protocol used for Table 2.02 (entry 1), it was found that the reaction of *β*-bromostyrene was finished in 4 h. The only side product of the reaction was trace amounts of the dimer resulting from homocoupling of the starting bromide. Hydrolysis of **1** and subsequent purification led to the desired ketone **3** in an excellent 96% yield.

Table 2.03 shows the results obtained with a range of vinyl halides and electron-rich olefins. In general, reactions featuring electron-rich bromides such as *p*-methoxy-*β*-bromostyrene were complete in slightly shorter times. Worthy of particular mention is the reaction of *p*-acetyl-*β*-bromostyrene (entry 7), **10** would be difficult to achieve via a conventional aldol methodology. In addition to BVE, 2-hydroxyethyl vinyl ether allowed access to cyclic ketals under identical conditions (entries 8-10). The formation of a protected ketone in this way could be potentially useful when chemoselectivity would otherwise be troublesome. Unfortunately, ketals bearing methoxy groups on the aromatic ring were somewhat unstable in solution

and traces of the corresponding ketone were detectable by ^{1}H NMR after several hours. For convenience, the 2-methoxy compound was hydrolysed and isolated as the ketone (entry 11).[84]

Table 2.03. Regioselective Heck vinylation of electron-rich olefins with Pd-dppp in DMSO[a]



Entry	X	Product	t (h)	Yield (%)	Entry	X	Product	t (h)	Yield (%)
1	Br	 **4**	4	96	10[b]	Br	 **12**	3	82
2	Br	 **5**	4	91	11	Br	 **6**	3	82
3	Br	 **3**	3	82	12[c]	Cl	 **5**	27	66
4	Br	 **6**	3	80	13[c]	Cl	 **3**	24	76
5	Br	 **7**	4	75	14[c]	Cl	 **6**	24	64
6	Br	 **8**	4	70	15[c]	Cl	 **4**	27	70
7	Br	 **9**	5	65	16[c]	Br	 **13**	16	80
8[b]	Br	 **10**	4	97	17[c]	Br	 **14**	20	65[d]
9[b]	Br	 **11**	4	86					

[a] 1 mmol aryl bromide (1 mmol), BVE (3 mmol), Pd(OAc)$_2$ (3 mol%), dppp (6 mol%), NEt$_3$ (3 mmol) in 2 mL DMSO at 115 °C. Following the coupling reaction, HCl was added at rt. for 30 min. Isolated yields. No β-vinylation product was detected by ^{1}H NMR. [b] As in *a* but without hydrolysis. [c] Conditions as in *a* but Pd(OAc)$_2$ (5 mol%) and dppp (10 mol%) used. [d] Conversion measured by ^{1}H NMR.

Remarkably, vinyl chlorides also reacted, affording exclusively branched products, albeit in longer reaction times. Again, these products were hydrolysed and isolated as the ketones in good yields (entries 12-15). To our knowledge, these are the first examples of vinyl chlorides with an electron-rich olefin.

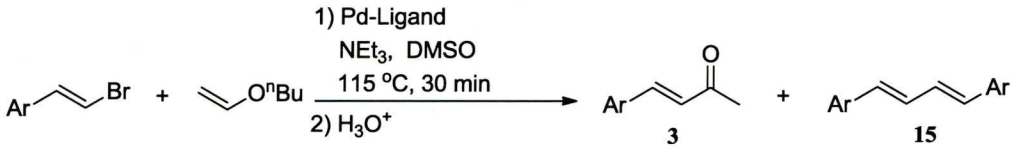
Another reaction that was interesting to us was that of 2-substituted vinyl ether with a vinyl halide as this would lead to products other than methyl ketones. However, reactions with these olefins, which are known to be less reactive, were much slower than with BVE.[95,96] Thus, even with the catalyst loading increased to 5 mol%, 1-propenyl ether took 16 h to complete (entry 16). With 1-butenyl ethyl ether, complete conversion could not be reached, even with long reaction times (entry 17).

Because reactions of substituted vinyl ethers were sluggish, it was decided to undertake a ligand screening. The results are shown in Table 2.04. Much to our surprise, the regioselectivity of the reaction was unaffected by the choice of ligand; be it monodentate or bidentate, the linear product was never detected. Only varying amounts of the homocoupling

products were produced.[97] Remarkably, the monophosphines significantly out-performed dppp, a ligand which has been universally used in regio-controlling of the Heck reaction of electron-rich olefins. Of the ligands tested, the bis(trifluoromethyl)-substituted PPh_3 (entry 4) and the hemilabile dpppO (entry 11) gave the best results, both affording ~95% conversion and complete selectivity for the desired products. Across the monophosphines, the bulkier ligands seemed to offer the higher ratio of Heck to homocoupling product. If this product is the result of a reductive homocoupling then this difference in selectivity can be rationalised by looking at the mechanism. After the oxidative addition the Pd(II)-vinyl species undergoes a

disproportionation reaction to $L_2Pd(II)$-$(vinyl)_2$ and $L_2Pd(II)$-X_2 complexes. This process will be more difficult with steric bulk around the metal centre impeding the approach of the complexes to one another.

Table 2.04. Ligand effects on the Heck vinylation of BVE[a]



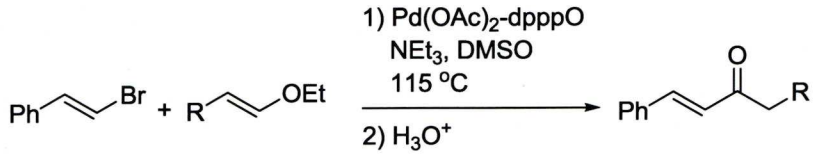
Entry	Ligand	Conversion (%)	Selectivity **3:15**
1	PPh_3	80	80:20
2	$P(4\text{-}OMePh)_3$	86	90:10
3	$P(2\text{-}OMePh)_3$	86	90:10
4	$P[3,5\text{-}(CF_3)_2Ph]_3$	94	>99:1
5	PCy_3	55	>99:1
6	dppm	37	>99:1
7	dppe	36	>99:1
8	dppp	61	>99:1
9	dppb	90	95:5
10	$(2\text{-}CF_3Ph)_2P(CH_2)_3P(2\text{-}CF_3Ph)_2$	86	>99:1
11	dpppO	95	>99:1

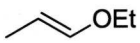
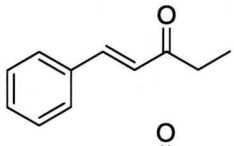
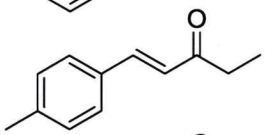
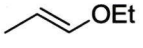
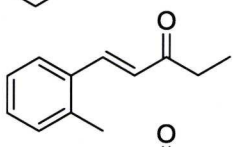
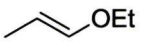
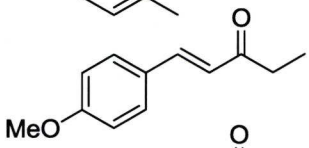
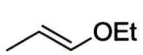
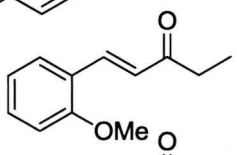
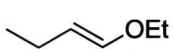
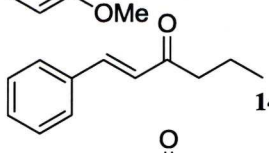
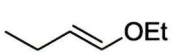
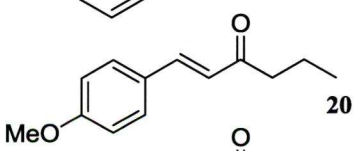
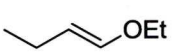
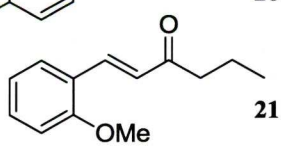
[a] Reaction conditions: *p*-methoxy-*β*-bromostyrene (1 mmol), BVE (3 mmol), $Pd(OAc)_2$ (3 mol%), monophoshine (9%) or bisphosphine (6%), NEt_3 (3 mmol) in 2 mL solvent at 115 °C

Encouraged by this success, we decided to continue the study of substituted vinyl ethers with dpppO as ligand, due to its lower cost and ease of availability compared to the monophosphine in entry 4.[98-100] In sharp contrast to dppp, dpppO allowed complete reactions of *p*-methoxy-*β*-bromostyrene with 1-propenyl and 1-butenyl ethyl ether in 0.75 and 4 h, respectively. The results from expanding the scope of this reaction are shown in Table 2.05. Good to excellent yields were obtained for a range of vinyl bromides in reaction times much shorter than those possible with dppp.

Lowering the quantity of catalyst, often based on expensive transition metals and ligands, is one of the main goals in making homogeneous catalysis greener and more economic. Hence, when we observed the high activity of Pd- dpppO in the reaction of 2-substituted vinyl ethers, we decided to investigate if a lower catalyst loading in the reactions of vinyl ethers would be feasible. Table 2.06 shows the results obtained with BVE and 2-hydroxyethyl vinyl ether. Much to our delight, the reactions at 1 mol% Pd (entries 1-8) were complete in around 1 h and those with 0.1 mol% Pd in 18 h (entries 9-11). It was noticed that, if left stirring overnight, the yield of the reaction of *p*-methoxy-*β*-bromostyrene with BVE dropped from 82 to ~35% (Table 2.03, entry 3). This indicates that the initially formed diene is unstable under the reaction conditions, explaining the lower yields observed with BVE at 0.1 mol% Pd loading (not shown). The ketals are seemingly much more stable under these conditions and excellent yields were obtained for all substrates. These results compare favourably with those shown in Table 2.03, and leave us with a highly selective and high-yielding protocol for the synthesis of *(E)*-*α,β*-unsaturated ketones as an alternative to other methods reported in the literature.

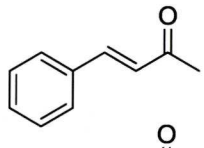
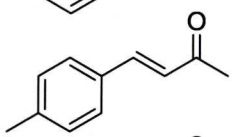
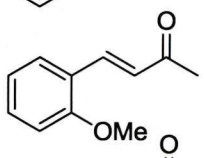
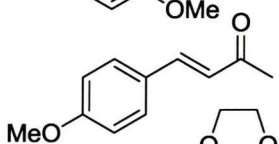
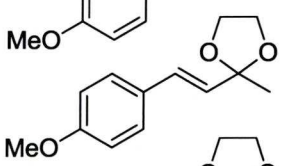
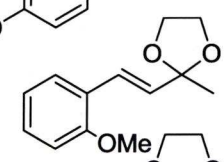
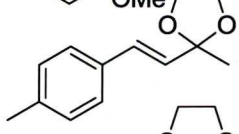
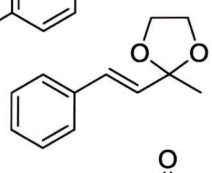
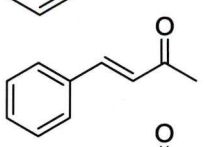
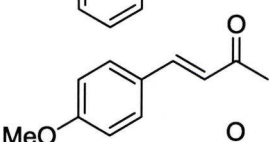
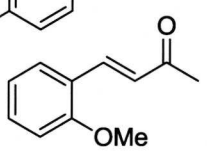
Table 2.05. Regioselective Heck vinylation of 2-substituted vinyl ethers[a]



Entry	Olefin	Product	t (h)	Yield (%)
1		 **13**	1	91
2		 **16**	1	76
3		 **17**	0.75	79
4		 **18**	1	77
5		 **19**	0.75	90
6		 **14**	5	86
7		 **20**	4	77
8		 **21**	4	80

[a] 1 mmol aryl bromide (1 mmol), BVE (3 mmol), $Pd(OAc)_2$ (5 mol%), dppp (10 mol%), NEt_3 (3 mmol) in 2 mL DMSO at 115 °C. Isolated yields given. No **2** or homocoupling type products were detected in the crude ^1H NMR.

Table 2.06. Regioselective Heck-vinylation of electron-rich olefins at reduced catalyst loading with Pd-dpppO[a]

Entry	Olefin	Product		t (h)	Yield (%)
1	O^nBu		**4**	1.25	84
2	O^nBu		**5**	1.25	97
3	O^nBu		**7**	1	90
4	O^nBu		**3**	1	92
5	$O(CH_2)_2OH$		**13**	1	92
6	$O(CH_2)_2OH$		**(7)**	1	88
7	$O(CH_2)_2OH$		**15**	1.25	82
8	$O(CH_2)_2OH$		**10**	1.25	95
9[b]	$O(CH_2)_2OH$		**4**	18	95
10[b]	$O(CH_2)_2OH$		**3**	18	93
11[b]	$O(CH_2)_2OH$		**7**	18	90

[a]Vinyl bromide (1 mmol), Olefin (3 mmol), $Pd(OAc)_2$ (1 mol%), dpppO (4 mol%), NEt_3 (3 mmol) in 2 mL DMSO at 115 °C. [b]As *a* but with $Pd(OAc)_2$ (0.1 mol%) and dpppO (0.4 mol%).

Although we were pleased with the results thus far, they raised an important question: Is the ionic pathway **A** or the neutral pathway **B** (Scheme 1.14) responsible for the observed products? It is generally accepted that the arylation of electron-rich olefins proceeds via a cationic mechanism (**A**, Scheme 1.14) and the related vinylation is judged under the same criteria, four of which exist in the literature to judge the feasibility of the mechanism. In order to shed some light on the vinylation we decided to see how the reaction behaves with respect to these criteria.

1. Bidentate ligands are required to obtain branched products when bromides are the aryl/vinylating agent.[78-82] However, as revealed in the ligand screening, not only were bidentate ligands unnecessary for regiocontrol, the monodentate or hemilabile phosphines gave significantly faster rates. This is surprising as the neutral pathway **B** would become more likely under these conditions.

2. The addition of halide ions to reactions in which the pathway **A** is thought to dominate inhibits the catalysis.[78,92,93] This is particularly evident from arylation work done in this group, where addition of as little as 10 mol% bromide halted the arylation of butyl vinyl ether.[89] However, Table 2.07 shows that the vinylations under question are relatively insensitive to additional halide. Most notably the reaction still proceeds in the presence of 200 mol% NBu_4Br, albeit at a reduced rate. Although they inhibited the catalysis to a greater degree than bromide, the reaction was still relatively insensitive to chloride ions.

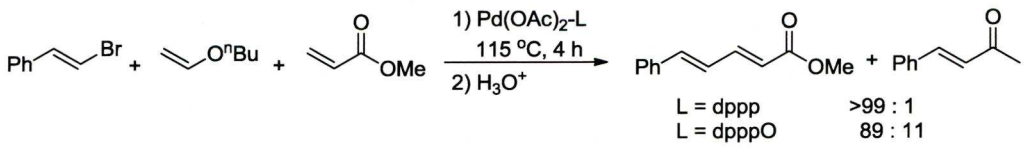
Table 2.07. Effect of halide ions on the vinylation of BVE with *p*-methoxy-*β*-bromostyrene[a]

		NBu_4Br		NEt_4Cl	
Entry	Additive[b]	Conversion[c] (%)	Selectivity[d]	Conversion (%)	Selectivity[e]
1	None	61	> 99:1	61	>99:1
2	10	58	> 99:1	32	>99:1
3	50	44	> 99:1	12	>99:1
4	200	17	> 99:1	<5	>99:1

[a]Reaction conditions: *p*-methoxy-*β*-bromostyrene (1 mmol), BVE (3 mmol), $Pd(OAc)_2$ (3 mol%), dppp (6 mol%), NEt_3 (3 mmol) in 2 mL solvent at 115 °C. [b] NBu_4Br or NEt_4Cl. [c] NBu_4Br. [d] Molar ratio of **1:2**. [e] NEt_4Cl.

3. The use of halide scavengers or ionic media enhances the selectivity and/or the rate of reactions where **A** is presumed to be the dominant pathway.[79,89,91,92,101] We found that, contrary to arylation studies, the vinylation was very slow in ionic liquids and negligible effect on the rate was observed in either [bmim][BF_4] or DMSO on addition of [$HNEt_3$][BF_4].

4. In a direct competition reaction between an electron-rich and an electron-deficient olefin, such as the one shown in Scheme 2.18, an electron-rich olefin would be more reactive when **A** is believed to prevail.[81,92] We found this was not the case when a reaction between a vinyl bromide and equimolar quantities of BVE and methyl acrylate was undertaken; regardless of the ligand chosen, *β*-vinylation of methyl acrylate was the dominant reaction.



Scheme 2.18. Competition reaction between an electron-rich and deficient olefin

All the results presented thus far were obtained with *(E)-β*-bromostyrenes. Further insight into the mechanism was gained by observations made with *(Z)-β*-bromostyrenes. The commercially available *β*-bromostyrene contains approximately 13% *cis* isomer but, interestingly, our products contained >99% *trans* olefins in all the reactions aforementioned. This prompted us to investigate the reactions of the *cis* isomer. Using the same conditions as those shown in Table 2.03 (entry 3), *(Z)-p*-methoxy-*β*-bromostyrene was reacted with BVE. Even with a starting material with an *Z:E* ratio of >19:1, the *E* isomer was obtained exclusively according to NMR. This selectivity for the *trans* product may be attributed to a Pd-catalysed isomerisation during/after oxidative addition (*vide infra*).[102] In support of this proposition, no change in the *cis:trans* ratio of the free vinyl halide was observed when the starting material was subjected to the coupling reaction conditions in the absence of olefin.

The kinetic profiles of the two starting isomers reacting with BVE are shown in Figure 2.01, revealing insignificant difference between them in rates. Amatore and Jutand showed that *cis* vinyl bromides are significantly slower at oxidative addition than their *trans* counterparts.[103] Hence, the similarity in rates appears to rule out oxidative addition as rate determining in the Heck vinylation. Further evidence for this is the faster reactions of vinyl bromides with electron-donating groups on the aryl ring. If oxidative addition were rate limiting these compounds would be

expected to react slower. As with arylation reactions, the vinylation under question may be rate limited by the migratory insertion.[92,104]

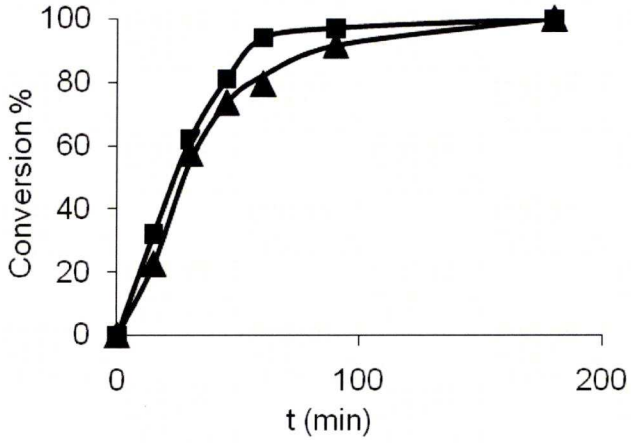
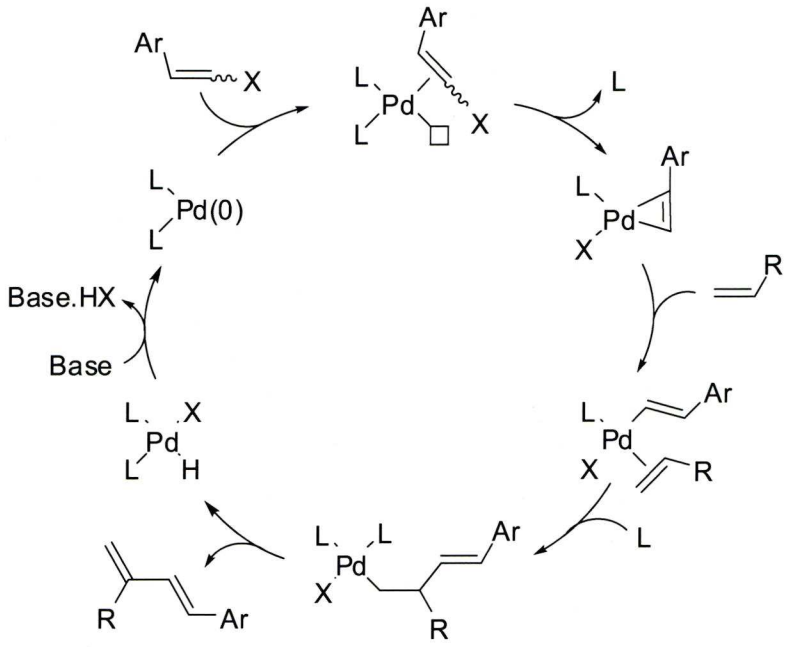


Figure 2.1. Reaction profiles of *cis/trans p*-methoxy-*β*-bromostyrene reacting with BVE in DMSO. ■ *trans*; ▲ *cis*. Reaction conditions: 1 mmol bromide, 3 mmol BVE, 3 mol% $Pd(OAc)_2$, 6 mol% dppp, 3 mmol NEt_3 in DMSO at 115 °C.

The combination of all the pieces of evidence presented above leads us to believe that the regioselective internal vinylation of electron-rich olefins is more likely to proceed via the neutral pathway **B**. Hence, a modified mechanism for the reaction is proposed and shown in Scheme 2.19. Oxidative addition of the vinyl halide to a Pd(0) leads to an η^2 vinyl species. It is proposed that this proceeds via dissociation of a *neutral* ligand and η^2 coordination of the vinyl ligand. The incoming olefin then displaces the η^2 vinyl group, rendering it η^1 coordinating. Regardless of the geometry of the starting vinyl halide, the change in the coordination mode is expected to lead to a more stable *trans* palladated olefin and thus the *trans* selectivity observed above.[102] The usual process of insertion, *β*-hydride elimination and

reductive elimination of HX then follows, regenerating the active Pd(0) catalyst and completing the catalytic cycle.

Scheme 2.19. Proposed neutral pathway for the Heck vinylation of electron-rich olefins



DFT calculations by Deeth and Brown have shown that for a vinyl group migrating to a vinyl ether, α-substitution is preferred even for a neutral Pd species.[105] The calculations with a monodentate phosphine show a energy difference for the linear/branched transition states of 6 kJ mol^{-1}, corresponding to a 60:40 product distribution in favour of the branched alkene. Although somewhat more pronounced in our case, this bias is in agreement with our experimental findings. We note, however, the work of Amatore and Jutand, who showed that cationic $[Pd(dppp)Ar(solvent)]^+$ is more reactive towards olefins than the analogous [Pd(dppp)(Ar)X].[104] They have also recently demonstrated that, for arylation in DMF, the insertion step always proceeds in an ionic fashion i.e. from $[ArPd(dppp)(DMF)]^+$.[106] Whether or not this is the case for the vinylation in DMSO remains to be investigated.

2.3 Conclusions and Future Work

In summary, a highly efficient protocol for the Pd-catalysed regioselective Heck vinylation of electron-rich olefins has been developed. Initially a Pd-dppp catalyst allowed for the reaction of vinyl bromides and chlorides with BVE to yield, after hydrolysis, (*E*)-4-aryl-but-3-en-2-ones in good to excellent yields (up to 97%). Hydroxyalkyl vinyl ethers also reacted to yield the unsaturated ketals, also in excellent yields. We have also demonstrated the first examples of vinyl chlorides reacting with electron rich olefins. Because of the lower reactivity of 2-substituted vinyl ethers a ligand screening was undertaken and revealed that, contrary to arylation, monodentate and hemilabile phosphines were beneficial. Expedient reactions of less reactive olefins were achieved with the new catalyst system and reactions with terminal olefins were able to complete with just 0.1% Pd loading.

A mechanistic investigation was prompted by the remarkable selectivity exhibited by the vinyl halides studied. Evidence gathered from halide inhibition, ligand studies, ionic liquid reactions and a competition reaction suggests that the vinylation proceeds via a different mechanism to that of the related arylation. It is likely that the neutral pathway is in operation and responsible for α substitution. However, the ionic pathway cannot be ruled out, particularly when dppp is the ligand. Together with the results obtained from the study of cis/trans vinyl bromides, we have used this evidence to suggest a new mechanism for the Heck vinylation of electron-rich olefins that includes an isomerisation of the starting alkene to yield exclusive *trans* products.

It is clear from this work that there is a fundamental difference in the arylation and vinylation of electron rich olefins using a palladium catalyst. Future work would attempt to discover the origin of this difference through experimental

and theoretical studies. Stoichiometric NMR studies and DFT calculations are likely to be most useful.

The initial products of these reactions are dienes, substrates commonly employed in cycloaddition reactions. By coupling the reaction developed here with cycloaddition reactions such as Diels-Alder in one-pot procedures, high levels of molecular complexity could be built up in simple procedures from readily available starting materials. The hydrolysis products, α,β- unsaturated ketones are also extremely useful starting materials for a variety of reactions (*vide supra*) and could also be incorporated into one-pot procedures.

2.4 Experimental

Materials. All reactions were carried out under a nitrogen atmosphere. Chromatographic purifications were performed on silica gel (mesh 230-400) by the flash technique. 1-Butyl-3-methylimidizolium tetrafluoroborate ([bmim][BF_4]) was prepared according to the literature method.[1] Following vacuum-drying at 80 °C for 8 h, the ionic liquid was stored under nitrogen at ambient temperature. Triethylammonium tetrafluoroborate ([$HNEt_3$][BF_4]) was prepared according to the literature method.[2] DMSO was stored over 4 Å molecular sieves. $Pd(OAc)_2$, dppp, butyl vinyl ether (BVE), 1-propenyl and 1-butenyl ethyl ether, 2-hydroxy ethyl vinyl ether, methyl acrylate, triethylamine and β-bromostyrene were purchased from commercial sources and used as received. *Cis*[3] and *trans*[4] vinyl bromides were synthesised according to literature procedure, as was dpppO.[5] ^1H and ^{13}C NMR spectra were recorded at 400 (^1H), 100 (^{13}C) MHz in ppm with reference to TMS as an internal standard in $CDCl_3$ (unless otherwise stated). Mass spectra were obtained by chemical ionization (CI) unless otherwise stated. All compounds were characterised by ^1H and ^{13}C NMR, MS, HRMS and, where possible, elemental

analysis. Data was compared to literature values where this information was available.

General procedure for the Heck vinylation of terminal vinyl ethers with a Pd-dppp catalyst. An oven-dried, two-necked round-bottom flask containing a stir bar was charged with $Pd(OAc)_2$ (0.03 mmol, 7 mg), dppp (0.06 mmol, 25 mg), *β*-bromostyrene (1 mmol, 183 mg, 0.12 ml) and 2 mL DMSO. Following degassing three times, BVE (3 mmol, 301 mg, 0.36 mL) and NEt_3 (3 mmol, 303 mg, 0.4 mL) were injected sequentially. The flask was placed in a parallel reactor at 115 °C and stirred for an appropriate time. After cooling to room temperature, a small sample was taken for NMR analysis. 10 mL 10% HCl was then added (except when 2-hydroxy ethyl vinyl ether was used) and the solution extracted with 3x15 mL DCM. The combined organic layers were washed to neutrality with H_2O, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The α,*β*-unsaturated methyl ketone product (or cyclic ketal) was isolated from the crude mixture by chromatography on silica gel using ethyl acetate and hexane (1/99 to 10/90) as eluent.

General procedure for the Heck vinylation of 2-substituted vinyl ethers using a Pd-dpppO catalyst. An oven-dried, two-necked round-bottom flask containing a stir bar was charged with $Pd(OAc)_2$ (0.03 mmol, 7 mg), dpppO (0.1 mmol, 52 mg), *β*-bromostyrene (1 mmol, 183 mg, 0.12 mL) and 2 mL DMSO . Following degassing three times, NEt_3 (3 mmol, 303 mg, 0.4 mL) was injected and the flask was placed in a parallel reactor at 115 °C. After 3-4 min, 1-propenyl ethyl ether (3 mmol, 258 mg, 0.33 mL) was injected and the mixture was stirred for an appropriate time. After cooling to room temperature, a small sample was taken for NMR analysis. 10 mL 10% HCl was then added and the solution extracted with 3x15 mL DCM. The

combined organic layers were washed to neutrality with H_2O, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The α,*β*-unsaturated methyl ketone product was isolated from the crude mixture by chromatography on silica gel using ethyl acetate and hexane (1/99 to 5/95) as eluent.

General procedure for the Heck vinylation of terminal olefins at low catalyst loadings with Pd-dpppO. An oven-dried, two-necked round-bottom flask containing a stir bar was charged with $Pd(OAc)_2$ (0.01 mmol, 2 mg), dpppO (0.04 mmol, 9 mg), β-bromostyrene (1 mmol, 183 mg, 0.12 mL) and 2 mL DMSO. Following degassing three times the mixture was stirred at room temperature until a bright yellow colour developed (5-10 min). BVE (3 mmol, 301 mg, 0.36 mL) and NEt_3 (3 mmol, 303 mg, 0.4 mL) were injected sequentially. The flask was placed in a parallel reactor at 115 °C and stirred for an appropriate time. The flask was removed, cooled to room temperature and a small sample taken for NMR analysis. 10 mL 10% $HCl_{(aq)}$ was added (except when 2-hydroxy ethyl vinyl ether was used) and the solution extracted with 3x15 mL DCM. The combined organic layers were washed to neutrality with H_2O, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The α,β-unsaturated ketone product was isolated from the crude mixture by chromatography on silica gel using ethyl acetate and hexane (1/99 to 5/95) as eluent.

General procedure for reactions used in the mechanistic study. An oven-dried, two-necked round-bottom flask containing a stir bar was charged with $Pd(OAc)_2$ (0.03 mmol, 7 mg), ligand (0.06 mmol for bis-phosphines, 0.09 mmol for monophosphines), *p*-methoxy-*β*-bromostyrene (1 mmol, 213 mg), salt additive (where appropriate) and 2 mL DMSO. Following degassing three times, BVE (3 mmol, 301 mg, 0.36 mL) and NEt_3 (3 mmol, 303 mg, 0.4 mL) were injected

sequentially. The flask was placed in a parallel reactor at 115 °C and stirred for 0.5 h. The flask was removed, cooled rapidly to room temperature under running cold water and 10 mL 10% $HCl_{(aq)}$ added immediately to stop the reaction. Following extraction with 3x15 mL DCM the combined organic layers were concentrated *in vacuo* and a sample of the crude mixture was used directly for ^{1}H NMR analysis to determine the selectivity and conversion.

Procedure for the competition reaction between butyl vinyl ether and methyl acrylate. An oven-dried, two-necked round-bottom flask containing a stir bar was charged with $Pd(OAc)_2$ (0.03 mmol, 7 mg), dppp (0.06 mmol, 25 mg), *β*-bromostyrene (1 mmol, 183 mg, 0.12 mL) and 2 mL DMSO. Following degassing three times BVE (1.5 mmol, 150 mg, 0.18 mL), methyl acrylate (1.5 mmol, 129 mg, 0.13 mL) and NEt_3 (3 mmol, 303 mg, 0.4 mL) were injected sequentially. The flask was placed in a parallel reactor at 115 °C and stirred for 3 h. TLC of the crude mixture confirmed that no starting material remained and no trace of the ketone product was visible. The flask was removed, cooled to room temperature and 10 mL 10% $HCl_{(aq)}$ added. Following extraction with 3x15 mL DCM, the combined organic layers were concentrated *in vacuo* and a sample of the crude mixture was used directly for ^{1}H NMR analysis.

2.5 Compounds characterised

N.B. For compounds where microanalysis data is not available the ^{1}H-NMR is provided as proof of >95 % purity in section 2.6.

(E)-4-Phenylbut-3-en-2-one. 4

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56-7.53 (m, 3H), 7.50 (d, J = 16.0 Hz, 1H), 7.41-7.39 (m, 2H), 6.72 (d, J = 16.0 Hz, 1H), 2.39 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.8, 143.9, 134.8, 131.0, 129.4, 128.7, 127.6, 28.0

HRMS Calcd for $C_{10}H_{11}O$ $(M + H)^+$: 147.0810. Found: 147.0813

Anal Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 82.18; H, 6.92

(*E*)-4-*p*-Tolylbut-3-en-2-one. 5

^{1}H NMR (400 MHz, DMSO-d^6) δ = 7.59 (d, J = 9.4 Hz, 2H), 7.56 (d, J = 16.3 Hz, 1H), 7.26 (d, J = 9.5 Hz, 2H), 6.74 (d, J = 16.3 Hz, 1H), 2.37 (s, 3H), 2.33 (s, 3H)

^{13}C NMR (100 MHz, DMSO-d^6) δ = 198.3, 144.0, 141.9, 133.6, 130.9, 129.6, 127.7, 27.8, 21.8

HRMS Calcd for $C_{11}H_{13}O$ $(M + H)^+$: 161.0967. Found: 161.0972

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.31; H, 7.58

(*E*)-4-(4-Methoxyphenyl)but-3-en-2-one. 3

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 (d, J = 8.7 Hz, 2H), 7.47 (d, J = 16.3 Hz, 1H), 6.92 (d, J = 8.7 Hz, 2H), 6.61 (d, J = 16.3 Hz, 1H), 3.84 (s, 3H), 2.35 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.7, 162.1, 143.6, 130.4, 127.6, 125.5, 114.9, 55.8, 27.8

HRMS Calcd for $C_{11}H_{13}O_2$ $(M + H)^+$: 177.0916. Found: 177.0911

Anal Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.72; H, 6.84

(*E*)-4-(2-Methoxyphenyl)but-3-en-2-one. 6

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (d, J = 16.5 Hz, 1H), 7.55-7.53 (m, 1H), 7.38-7.34 (m, 1H), 6.99-6.91 (m, 2H), 6.75 (d, J = 16.5 Hz, 1H), 3.90 (s, 3H), 2.38 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.4, 158.7, 139.1, 132.1, 128.8, 128.2, 123.9, 121.3, 111.6, 55.9, 27.5

HRMS Calcd for $C_{11}H_{13}O_2$ $(M + H)^+$: 177.0916. Found: 177.0911

Anal Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.79; H, 7.00

***(E)*-4-(4-Chlorophenyl)but-3-en-2-one. 7**

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 16.3 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 16.3 Hz, 1H), 2.37 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.4, 142.2, 136.9, 133.4, 129.8, 129.7, 128.0, 28.0HRMS Calcd for $C_{10}H_{10}ClO$ $(M + H)^+$: 181.0420 Found: 181.0422

Anal Calcd for $C_{10}H_{10}ClO$: C, 66.49; H, 5.02. Found: C, 66.73; H, 5.10

***(E)*-4-(4-Fluorophenyl)but-3-en-2-one 8**

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56-7.51 (m, 2H), 7.48 (d, J = 16.3 Hz, 1H), 7.11-7.06 (m, 2H), 6.64 (d, J = 16.3 Hz, 1H), 2.36 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.4, 164.5 (d, $^1J_{CF}$ = 252 Hz), 142.4, 131.1 (d, $^4J_{CF}$ = 3 Hz), 130.5 (d, $^3J_{CF}$ = 9 Hz), 127.3, 116.5 (d, $^2J_{CF}$ = 22 Hz), 28.0

HRMS Calcd for $C_{11}H_{10}OF$ $(M + H)^+$: 165.0716. Found: 165.0715

Anal. Calcd for $C_{10}H_9FO$: C, 73.16; H, 5.53. Found: C, 72.84; H, 5.61

(*E*)-4-(4-Acetylphenyl)but-3-en-2-one. 9

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 16.3 Hz, 1H), 6.72 (d, J =16.3 Hz, 1H), 2.55 (s, 3H), 2.34 (s, 3H);

^{13}C (100 MHz, $CDCl_3$) δ = 197.3, 196.6, 140.6, 137.2, 132.0, 128.1, 127.3, 125.6, 26.8, 25.7

HRMS calcd. For $C_{12}H_{12}O_2$: 188.0837 Found: 188.0842.

***(E)*-2-Methyl-2-styryl-1,3-dioxolane. 10**

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39-7.37 (m, 2H), 7.32-7.28 (m, 2H), 7.25-7.21 (m, 1H), 6.70 (d, J = 16.0 Hz, 1H), 6.15 (d, J = 16.0 Hz, 1H), 4.01-3.91 (m, 2H), 1.55 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 136.7, 130.2, 130.1, 128.8, 128.2, 127.4, 108.1, 65.1, 25.6

HRMS Calcd for $C_{12}H_{15}O_2$ $(M + H)^+$: 191.1072 Found: 191.1074

Anal Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.57; H, 7.45

***(E)*-2-Methyl-2-(4-methylstyryl)-1,3-dioxolane.11**

^1H NMR (400 MHz, $CDCl_3$) 7.27 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 6.66 (d, J = 16.1 Hz, 1H), 6.07 (d, J = 16.1 Hz, 1H), 4.00-3.95 (m, 2H), 3.95-3.91 (m, 2H), 2.32 (s, 3H), 1.54 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 138.1, 133.8, 129.9, 129.6, 129.1, 127.0, 108.1, 64.0, 25.6, 21.5

HRMS Calcd for $C_{13}H_{17}O_2$ $(M + H)^+$: 205.1229. Found: 205.1232

Anal Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.30; H, 7.95

***(E)*-2-(4-Methoxystyryl)-2-methyl-1,3-dioxolane. 12**

^1H NMR (400 MHz, $CDCl_3$) δ = 7.32 (d, J = 16.1 Hz, 1H), 6.85 (d, J = 8.1 Hz, 2H), 6.63 (d, J = 8.1 Hz, 2H), 6.00 (d, J = 16.1 Hz, 1H), 4.10-4.00 (m, 2H), 4.00-3.90 (m, 2H), 3.80 (s, 3H), 1.55 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.9, 129.6, 129.4, 128.4, 114.4, 108.2, 65.0, 64.1, 55.7, 25.7

HRMS Calcd for $C_{13}H_{17}O_3$ $(M + H)^+$: 221.1178; Found: 221.1184.

Anal Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.67; H, 7.34

***(E)*-1-Phenylpent-1-en-3-one 13**

^1H NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, J = 16.1 Hz, 1H), 7.62-7.54 (m, 2H), 7.39-7.37 (m, 3H), 6.74 (d, J = 16.1 Hz, 1H), 2.69 (q, J = 7.3 Hz, 2H), 1.17 (t, J = 7.3 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.3, 142.6, 135.1, 130.7, 129.3, 128.6, 126.5, 34.4, 8.6.

HRMS Calcd for $C_{11}H_{13}O$ $(M + H)^+$: 161.0966. Found: 161.0968

***(E)*-1-p-tolylpent-1-en-3-one 16**

^1H NMR (400 MHz, $CDCl_3$) δ = 7.53 (d, *J* = 16.1 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.70 (d, *J* = 16.1 Hz, 1H), 2.68 (q, *J* = 7.3 Hz, 2H), 2.37 (s, 3H), 1.17 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.3, 142.6, 141.3, 132.3, 130.1, 128.6, 125.6, 34.3, 21.8, 8.7

HRMS Calcd for $C_{12}H_{15}O$ $(M + H)^+$: 175.1123. Found: 175.1124

***(E)*-1-o-tolylpent-1-en-3-one. 17**

^1H NMR (400 MHz, $CDCl_3$) δ = 7.86 (d, *J* = 16.0 Hz, 1H), 7.57-7.56 (m, 1H), 7.29-7.25 (m, 1H), 7.22-7.19 (m, 2H), 6.67 (d, *J* = 16.0 Hz, 1H), 2.69 (q, *J* = 7.3 Hz, 2H), 2.44 (s, 3H), 1.18 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.2, 140.1, 138.3, 134.0, 131.2, 130.5, 127.4, 126.8, 34.8, 20.2, 8.6

HRMS Calcd for $C_{12}H_{15}O$ $(M + H)^+$: 175.1123. Found: 175.1127

***(E)*-1-(4-methoxyphenyl)pent-1-en-3-one 18**

^1H NMR (400 MHz, $CDCl_3$) δ = 7.52 (d, *J* = 16.0 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.63 (d, *J* = 16.0 Hz, 1H), 3.84 (s, 3H), 2.67 (q, *J* = 7.4 Hz, 2H), 1.16 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.3, 162.0, 142.4, 130.3, 127.9, 124.3, 114.8, 55.7, 34.3, 8.8

HRMS Calcd for $C_{12}H_{15}O_2$ $(M + H)^+$: 191.1072. Found: 191.1078

(*E*)-1-(2-Methoxyphenyl)pent-1-en-3-one. 19

^1H NMR (400 MHz, $CDCl_3$) δ = 7.90 (d, *J* = 16.4 Hz, 1H), 7.55-7.52 (m, 1H), 7.36-7.32 (m, 1H), 6.97-6.90 (m, 2H), 6.78 (d, *J* = 16.4 Hz, 1H), 3.87 (s, 3H), 2.70 (q, *J* = 7.3 Hz, 2H), 1.16 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.9, 158.8, 137.9, 132.0, 128.8, 127.2, 124.0, 121.2, 111.6, 55.9, 33.9, 8.8

HRMS Calcd for $C_{12}H_{15}O_2$ $(M + H)^+$: 191.1072. Found: 191.1074

***(E)*-1-Phenylhex-1-en-3-one. 14**

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 16.2 Hz, 1H), 7.58-7.57 (m, 2H), 7.41-7.37 (m, 3H), 6.74 (d, *J* = 16.2 Hz, 1H), 2.64 (t, *J* = 7.4 Hz, 2H), 1.81-1.65 (m, 2H), 1.97 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 200.8, 142.7, 135.1, 130.7, 129.3, 128.6, 126.8, 43.2, 18.2, 14.2

HRMS Calcd for $C_{12}H_{15}O$ $(M + H)^+$: 175.1123. Found: 175.1121

***(E)*-1-(4-methoxyphenyl)hex-1-en-3-one 20**

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (d, *J* = 16.2 Hz, 1H), 7.42 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.56 (d, *J* = 8.7 Hz, 2H), 3.76 (s, 3H), 2.55 (t, *J* = 7.4 Hz, 2H), 1.66-1.60 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.0, 161.9, 142.5, 130.3, 127.9, 124.6, 114.0, 55.8, 43.1, 18.4, 14.2

HRMS Calcd for $C_{13}H_{17}O_2$ $(M + H)^+$: 205.1229. Found: 205.1235

***(E)*-1-(2-methoxyphenyl)hex-1-en-3-one. 21**

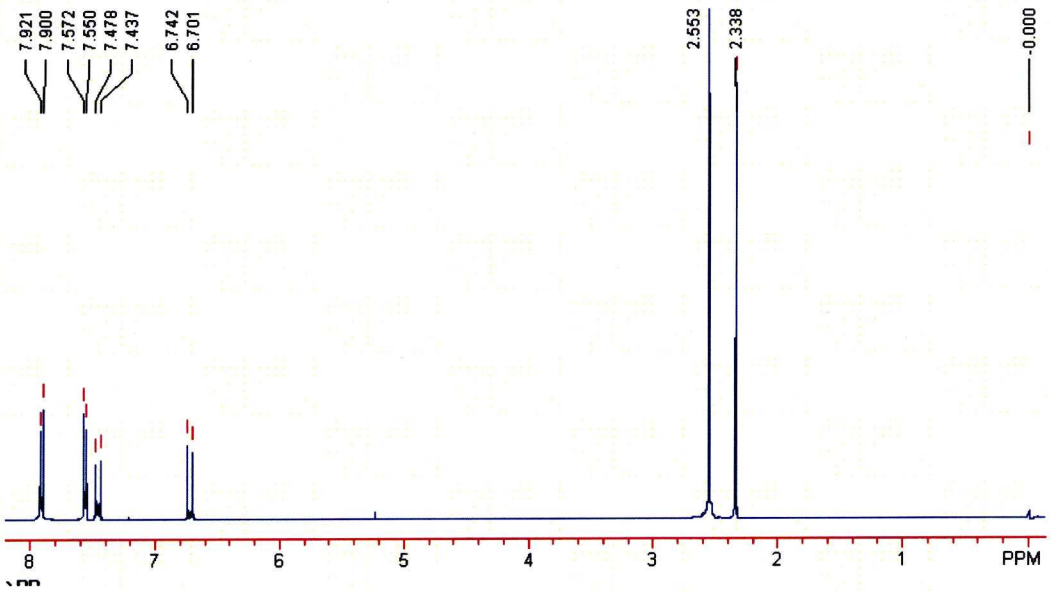
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 (d, *J* = 16.3 Hz, 1H), 7.55-7.53 (m, 1H), 7.37-7.33 (m, 1H), 6.98-6.90 (m, 2H), 6.77 (d, *J* = 16.3 Hz, 1H), 3.89 (s, 3H), 2.65 (t, *J* = 7.4 Hz, 2H), 1.74-1.69 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.5, 158.8, 138.0, 132.0, 128.8, 127.5, 124.1, 121.2, 111.6, 55.9, 42.7, 18.3, 14.3

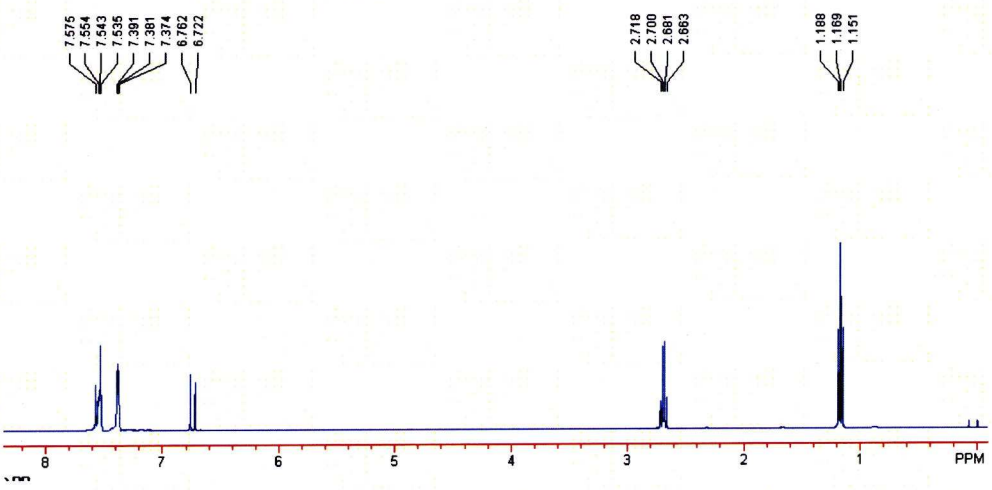
HRMS Calcd for $C_{13}H_{17}O_2$ $(M + H)^+$: 205.1228. Found: 205.1234

2.6 ^{1}H-NMR spectra

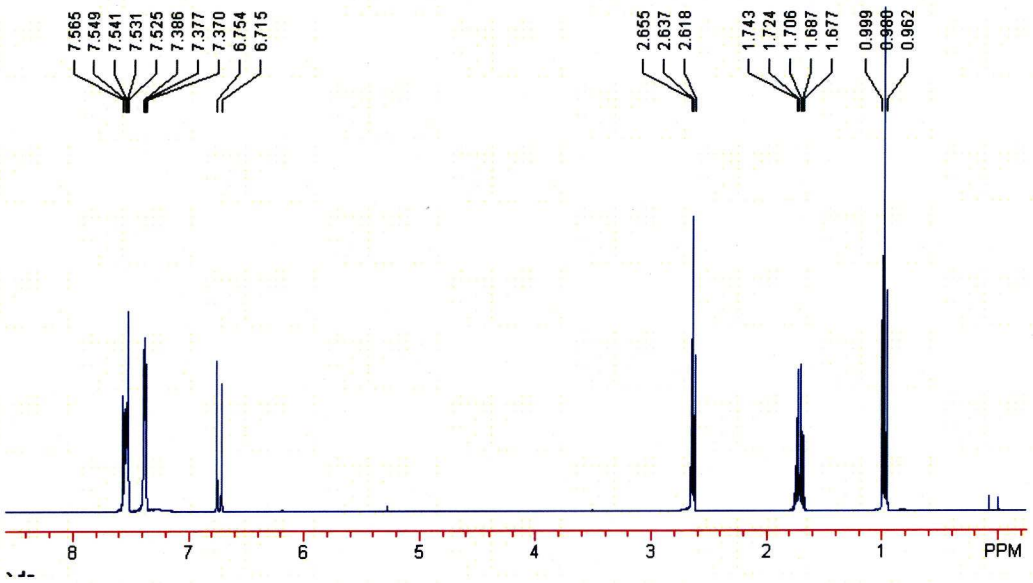
(*E*)-4-(4-Acetylphenyl)but-3-en-2-one. 9



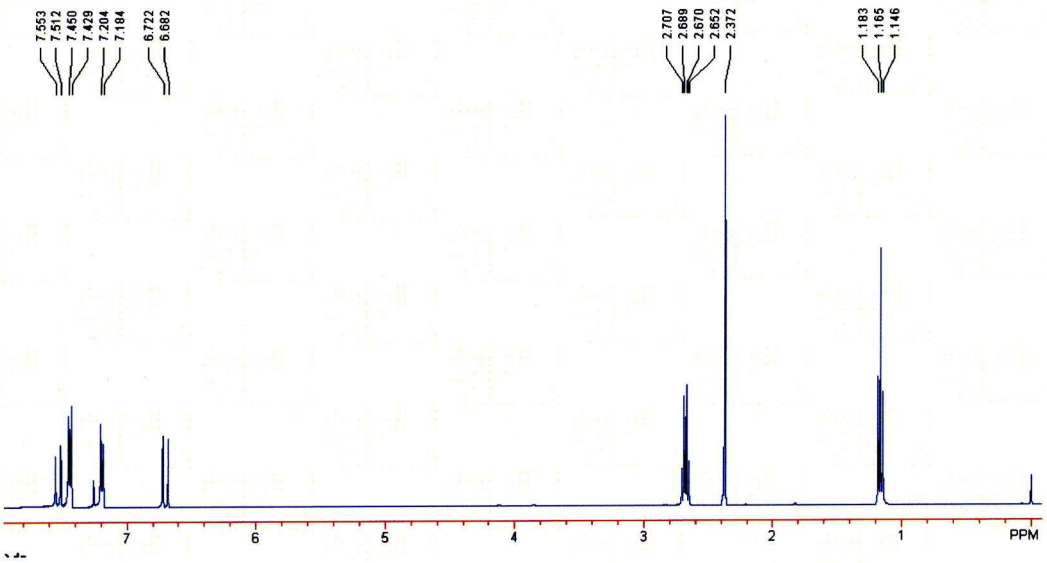
(E)-1-Phenylpent-1-en-3-one 13



(*E*)-1-Phenylhex-1-en-3-one. 14



(*E*)-1-p-tolylpent-1-en-3-one. 16



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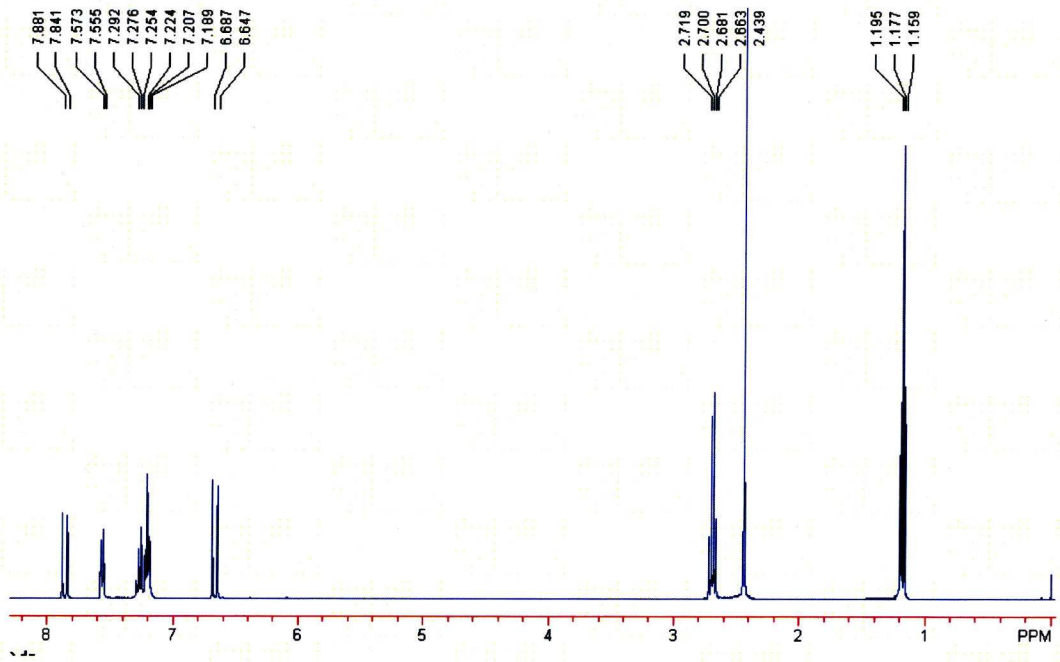
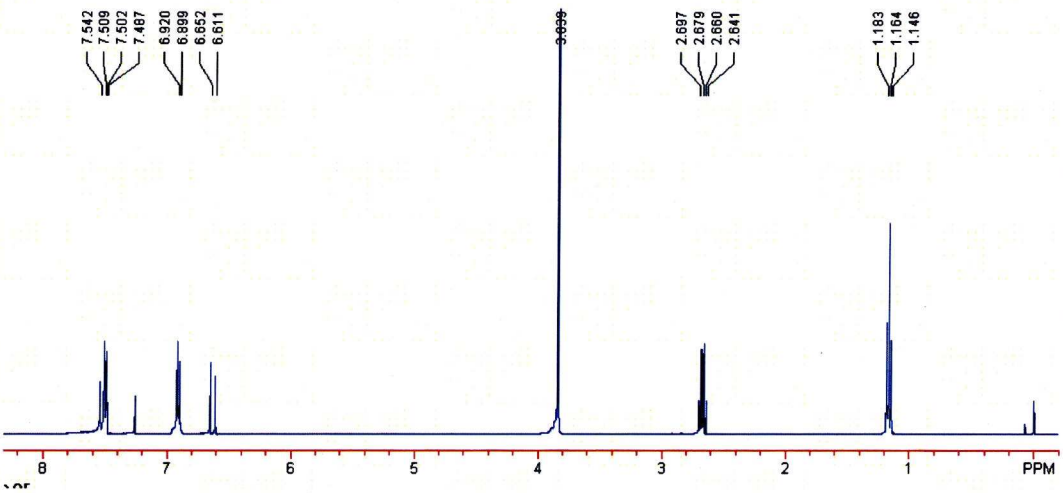
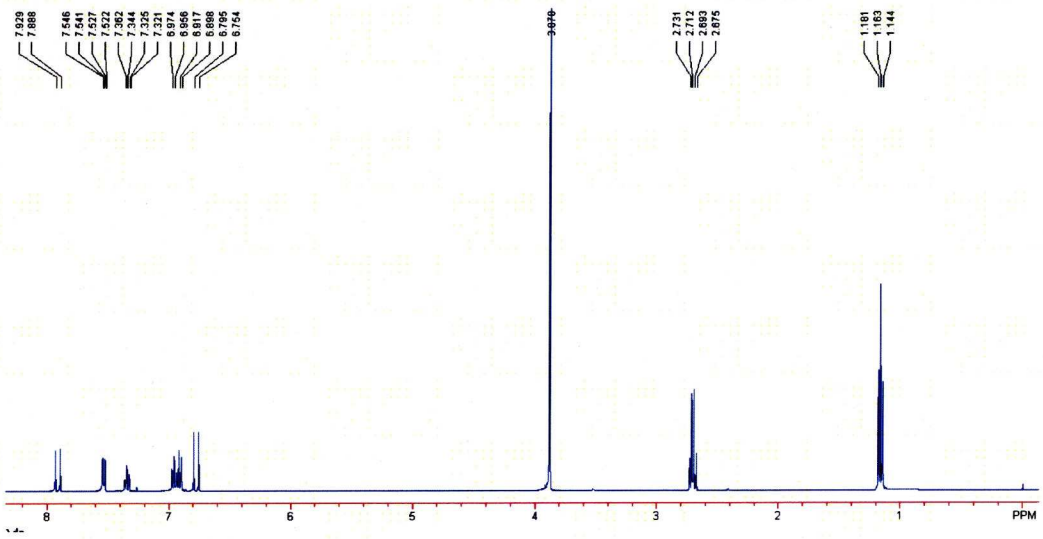


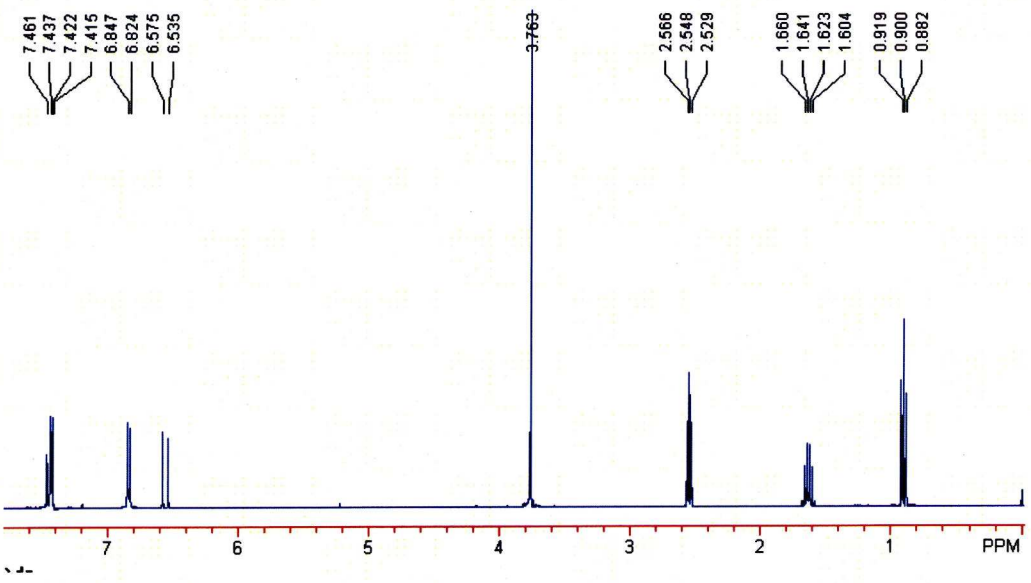
(*E*)-1-(4-methoxyphenyl)pent-1-en-3-one 18



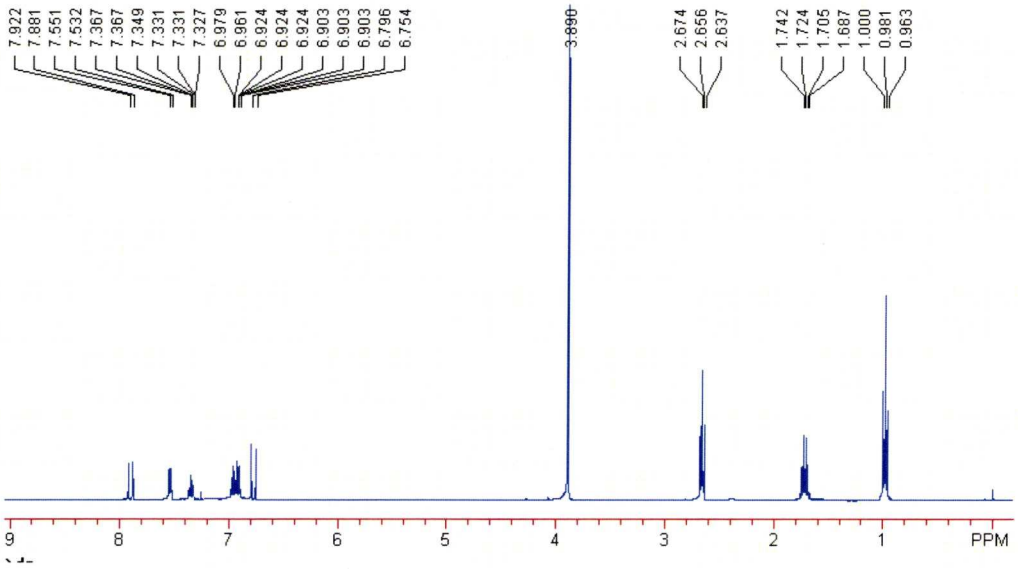
(*E*)-1-(2-Methoxyphenyl)pent-1-en-3-one. 19



***(E)*-1-(4-methoxyphenyl)hex-1-en-3-one 20**



(*E*)-1-(2-methoxyphenyl)hex-1-en-3-one. 21



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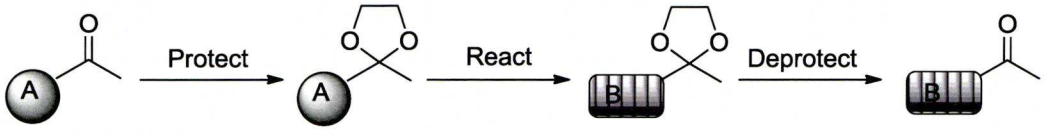
Chapter 3

Regioselective Heck reactions in Diols and Cascade Formation of Cyclic Ketals

3.1 Introduction

Cyclic Ketals- Application

Cyclic ketals (or acetals) are without doubt most famous in organic chemistry as protecting groups.[1] They are easily prepared from the parent aldehyde or ketone (*vide infra*), can withstand a variety of reaction conditions and are easily removed after the desired reaction has taken place (Scheme 3.01).



Scheme 3.01. Cyclic ketals as protecting groups

Cyclic ketals also have an interesting profile of biological activity, selected examples are shown in Figure 3.01. This makes them a valid target for synthesis as well as a tool in the box for organic chemists wishing to protect carbonyl groups. Until recently, cyclic ketals have mainly been investigated and applied as antifungal agents. Ketoconazole is an antifungal agent with a variety of applications. As a topical application it is the active ingredient in medicated shampoos for the treatment of seborrheic dermatitis (dandruff) and considered safe enough to be sold as a non-prescription product.[2-4] As an oral medication, ketoconazole has an interesting role in the treatment of patients infected with HIV. Initially administered to treat opportunistic oral and gastrointestinal candidiasis, it was also found to have desirable

effects on the pharmacokinetics of the anti-retroviral drugs also taken by these patients.[5-7] Propiconazole is sprayed on crops to prevent fungal infections destroying them.[8, 9] Etoxadrol is a lead compound in the development of NMDA receptor antagonists, potential therapeutic agents for use in Alzheimer's disease, Parkinson's disease, epilepsy and other central nervous system disorders.[10] B-12, a derivative of ketoconazole, has been identified as a promising candidate for use as an antagonist of the human pregnane X receptor.[11] This receptor has been implicated in adverse drug reactions, increased cancer cell growth and drug resistance. B-12 has the advantage over ketoconazole of not stimulating CYP450 enzyme production and hence reduces the chance of unpredictable adverse drug reactions.

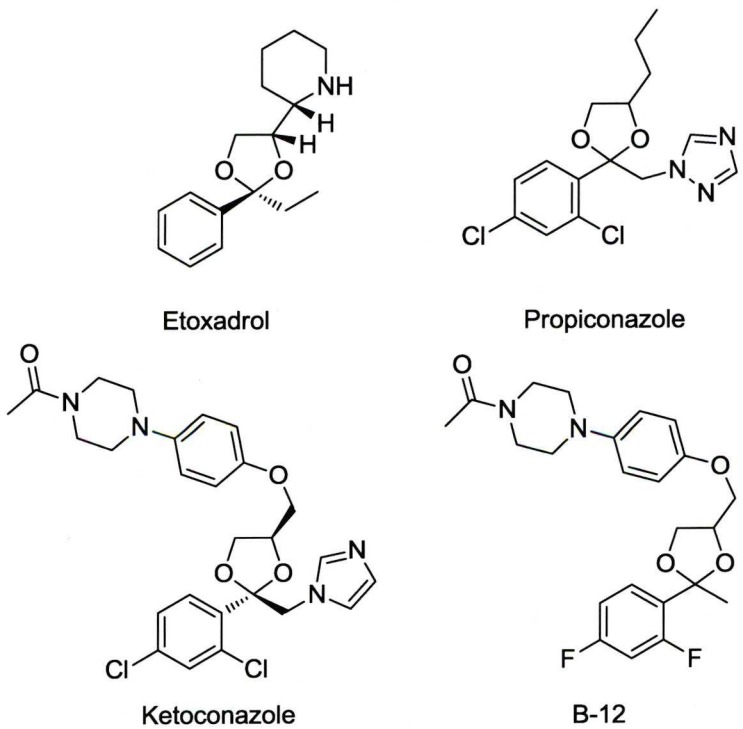
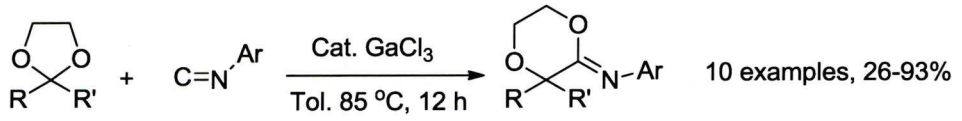


Figure 3.01. Cyclic ketals showing biological activity

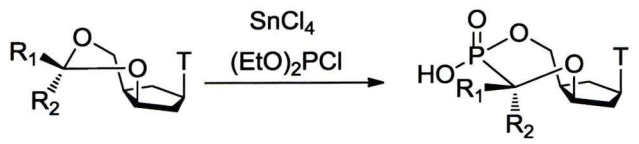
Aside from use as protecting groups, there are a few reports on the reactivity of the ketal ring itself. With ever more biologically relevant ketals emerging the

importance of reactions elaborating cyclic ketals can only increase. Chatani and co-workers discovered that, in the prescence of 10 mol% $GaCl_3$ at 80 °C, isocyanides could insert into the C-O bond of 5 and 6 membered ketals.[12] The reaction is selective for monoinsertion between C_2 and O with yields highly substrate dependant (Scheme 3.02).



Scheme 3.02. Insertion of isocyanides into cyclic ketals catalysed by $GaCl_3$

Rosenberg and co-workers utilised a ring expansion of cyclic ketals as a key step to synthesise novel nucleoside phostones.[13] In the presence of the lewis acid $SnCl_4$, chlorodiethyl phosphite reacts with 3,5 ketals derived from *xylo*-dT to produce the seven membered phostones in 86-91% yields (Scheme 3.03).

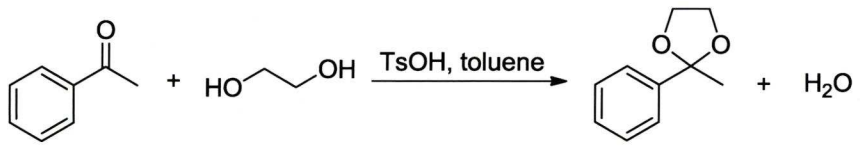


Scheme 3.03. Ring expansion of cyclic ketals for phostone synthesis

Cyclic Ketals- Synthesis

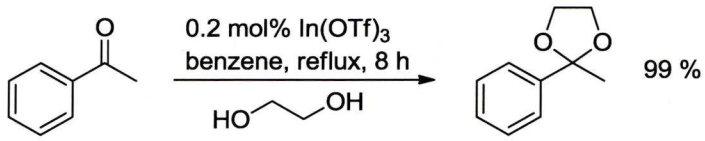
Many catalysts exist for the preparation of acetals/ketals from their parent carbonyl compounds.[14-28] A typical procedure for cyclic acetal/ketal synthesis involves the reaction of a ketone (or aldehyde) with a diol in the presence of a Brønsted acid catalyst combined with removal of the stoichiometric water produced.[1] Scheme 3.04 shows the ketalisation of acetophenone with ethylene glycol.

Toluenesulfonic acid in toluene with azeotropic distillation or a drying agent makes up a common catalyst system.



Scheme 3.04. TsOH catalysed ketal formation from acetophenone and ethylene glycol

Metal halides/triflates have gained a lot of attention for this purpose and systems comprising of $Ce(OTf)_3$, $Bi(OTf)_3$, $LaCl_3$ and $InCl_3$[19,27] have been reported. They can catalyse the reaction under neutral or nearly neutral conditions and hence are useful when acid-sensitive groups are present. A typical metal triflate catalysed example utilising $In(OTf)_3$[25] is shown in scheme 3.05.

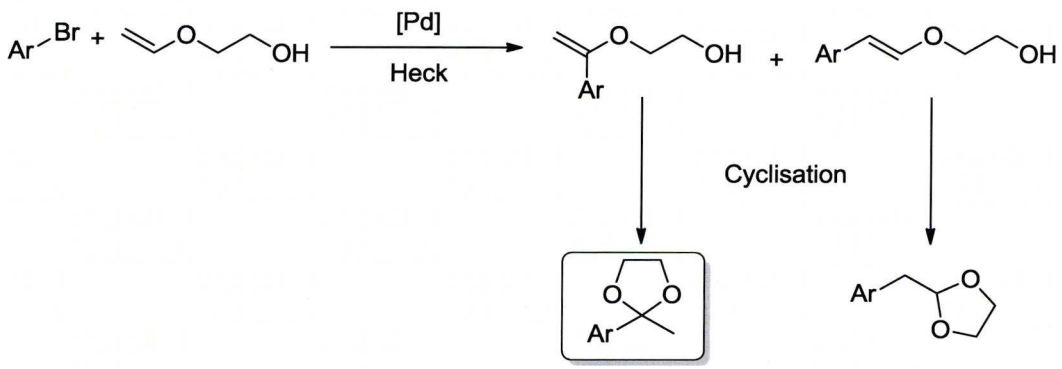


Scheme 3.05. $In(OTf)_3$ catalysed formation of the cyclic ketal of acetophenone

A rare example of acetelisation under basic conditions was reported by Mohan and co-workers who used $TiCl_4$ to form acetals and ketals in the presence of NEt_3.[23] The mild and efficient protocol allowed for a variety of carbonyl compounds to be protected. This was the first general method for protection of aldehydes and ketones under basic conditions. Another basic protocol that has proved versatile for cyclic acetal production is the Heck reaction of suitable electron-rich olefins.

Heck reaction for cyclic acetal/ketal synthesis

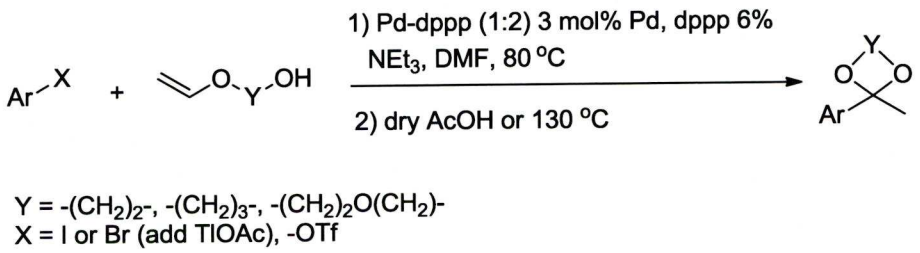
The Heck reaction of hydroxyalkyl vinyl ethers followed by cyclisation of the resulting aryl substituted olefins yields cyclic ketals/acetals.[31-35] The product obtained is dependant on the regioselectivity of the Heck reaction (Scheme 3.06). Hence, if arylation takes place at the α position of the olefin cyclisation affords cyclic ketals;[31, 33-35] β substitution leads to cyclic, aldehyde-derived acetals.[32] It is, therefore, necessary to control the regioselectivity of the Heck reaction to obtain the desired products. Generally the same tactics are used as for reactions of other electron-rich olefins.[33, 36-42] This method of ketal formation is favourable due to the operational simplicity, the basic environment and tolerance to the presence of carbonyl groups on the aryl ring. Further, it allows ketals to be synthesised from bromides instead of just carbonyls. Examples of cyclic ketal formation via regioselective Heck reaction are outlined below.



Scheme 3.06. Product dependency on the regioselectivity of Heck reactions

Hallberg and Larhed demonstrated the effectiveness of a Pd-dppp system for the α-arylation of a range of hydroxyalkyl vinyl ethers (Scheme 3.07).[31] For electron-rich (*p*-$OMeC_6H_5$) and electron-neutral (Ph) halides and triflates the cyclisation went smoothly to completion under the reaction conditions, the 5- and 7-

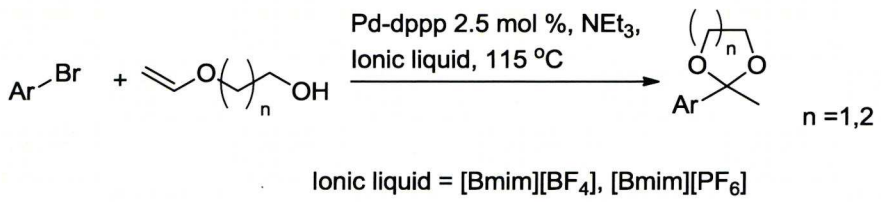
membered ketals being obtained in 62-84% yield. Diethylene glycol vinyl ether was also arylated and cyclised to the 9-membered ketal, albeit in a rather lower 33% yield. The instability of the ketal in the presence of silica during column chromatography is suspected to be responsible for this loss of product. For electron-deficient aryls, increasing the temperature to 130 °C or the addition of dry AcOH was necessary for complete ring closure, presumably due to the reduced basicity of the C-C double bond in these compounds. In cases where aryl halides were employed as arylating agents regioselectivity was achieved by the addition of TlOAc.[43] Some years later, as an extention of their work on preparing protected indanones,[44] the same researchers utilised the regioselective Heck reaction of hydroxyalkyl vinyl ethers for the synthesis of 3-aminoindan-1-ones.[45] The three component coupling reaction between salicylic aldehyde triflates, ethylene glycol vinyl ether and a secondary amine was later applied to the synthesis of active HIV-1 protease inhibitors.[46]



Scheme 3.07. Hallberg's conditions for regioselective Heck reaction of hydroxyalkyl vinyl ethers

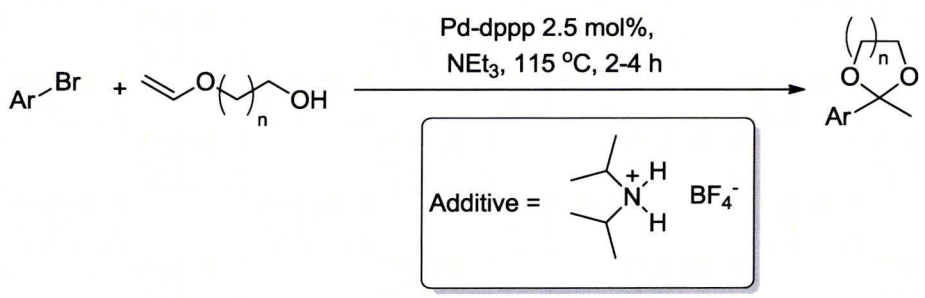
The ability of ionic liquids to promote regioselectivity in reactions of electron-rich olefins with aryl bromides was applied to the synthesis of 5- and 7-membered ketals by workers within this group.[35] A range of electron-rich and electron-deficient aryl bromides reacted with ethylene glycol vinyl ether in the presence of a $Pd(OAc)_2$/dppp/NEt_3 catalytic system (3/6/150 mol%) to afford the

cyclic ketals in 63-96% yield. Complete conversion was achieved in 8-30 h at 115 °C. 7-membered ketals, showed an equally wide scope but were isolated in slightly lower yields (61-86%) than the 5-membered analogues. The ionic liquid [Bmim][BF_4] as solvent negates the need for halide scavengers in these reactions allowing aryl bromides to be used as arylating agents. Particularly worthy of mention is that the catalyst and ionic liquid [bmim][PF_6] could be recycled eight times without significant drop in isolated yield.



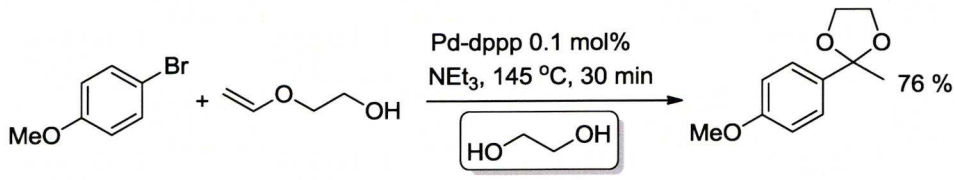
Scheme 3.08. Ionic liquids as solvents for regioselective ketal formation

Another 2006 publication by this group reported the use of H-bond donating salt additives as an alternative to halide scavengers such as TlOAc for arylations in molecular solvents.[33] The Pd-dppp catalyst (2.5 mol% Pd), prepared *in situ,* afforded cyclic ketals in 83-97 % yields in 2-4 h at 115 °C in DMF (Scheme 3.09). The additives increased the rate of arylation of hydroxyalkyl vinyl ethers in ionic liquids by approximately one order of magnitude.



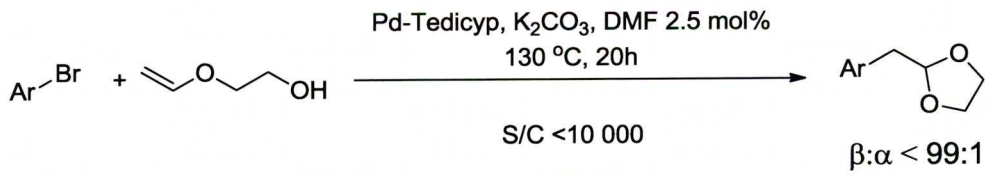
Scheme 3.09. H-Bond donors in regioselective ketal formation

Scheme 1.20 shows how the alcohol solvents can provide excellent regioselectivity for the arylation of electron-rich olefins.[34] The arylation of hydroxyalkyl vinyl ethers was achieved with Pd loadings as low as 0.1% in ethylene glycol (Scheme 3.10). The cyclic ketals were obtained in good yields after reaction times of just 30 min.



Scheme 3.10. Regioselective ketal formation at low catalyst loadings

The research group of Santelli used Pd in conjunction with the Tedicyp ligand previously mentioned to effect the β arylation of hydroxyl alkyl vinyl ethers.[32] The subsequent cyclisation afforded protected aryl acetaldehydes. The β:α regioselectivity was high (>99:1) for electron deficient substrates but dropped to as low as 66:34 for aryl bromides containg electron donating substituents. Yields of the products were generally high and substrate to catalyst ratios up to 10 000:1 possible for certain substrates.



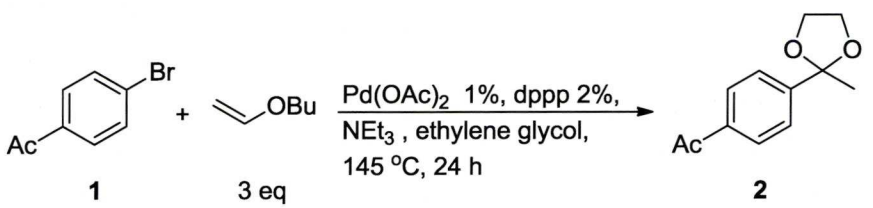
Scheme 3.11. Santelli's Pd-Tedicyp catalyst for β-selective arylation and arylacetaldehyde formation

Due to the importance of ketals and their increasing use in biological applications, there is always room for new methods of preparation, particularly those that can take place in a selective manner. Herein we report our finding on a new,

regioselective Heck arylation based method for the chemoselective formation of cyclic ketals.

3.2 Results and Discussion

During our continued studies of the Heck reaction of electron-rich olefins, a curious observation was made. If left stirring under the reaction conditions, the Pd-catalyzed Heck coupling between 4-bromoacetophenone **1** and butyl vinyl ether (BVE) in ethylene glycol eventually led to the corresponding cyclic ketal **2** (Scheme 3.12). This was surprising because, as discussed earlier, the use of hydroxyl vinyl ether is usually required to obtain such products.[31, 35] However, simple enol ethers are known to react with 1,2-diols such as those in carbohydrate chemistry as a means of protecting the latter.[47, 48] This raises a question about the observation made above; is **2** formed from a reaction of the arylated BVE with the solvent?

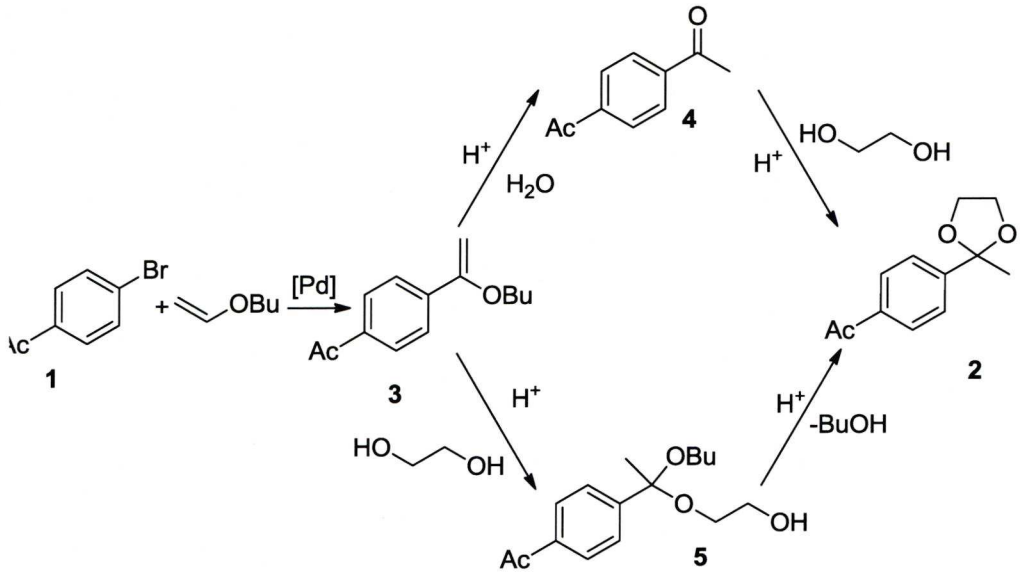


1 3 eq **2**

Scheme 3.12. Initial observation of the formation of **2** from **1**

Given that ethylene glycol vinyl ether is some fifty times more expensive than BVE (cheapest price per mL, Aldrich 2009), we thought the reaction in Scheme 3.12 might lead to a new method for easy ketal synthesis and therefore be worth pursuing. We envisaged two likely pathways for the reaction, proceeding via different intermediates with both acid-catalysed (Scheme 3.13). The first is hydrolysis of the initially formed enol ether **3** to the diketone **4** followed by a

classical ketalisation with the ethylene glycol solvent.[1] The second is acid-catalyzed formation of the mixed ketal **5** by addition of the solvent, followed by an intramolecular substitution reaction, eliminating butanol and generating **2.**



Scheme 3.13. Possible reaction pathways for cyclic ketals from enol ethers

^{1}H NMR and tlc monitoring of the reaction was undertaken in order to identify the reaction intermediates. No trace of **4** was detected by either method, making the hydrolysis/cyclisation pathway less likely. However, ^{1}H NMR showed that **5** was produced, increased and then decreased as formation of the ketal **2** was observed. A reaction profile is shown in Figure 3.02, showing that the Heck reaction to give the arylated BVE **3** is fast, **2** derives from **3** most likely via the intermediacy of **5**, and the overall reaction to give **2** appears to be limited by the cyclisation step. The intermediates **3** and **5** were characterized by stopping the reaction before completion.

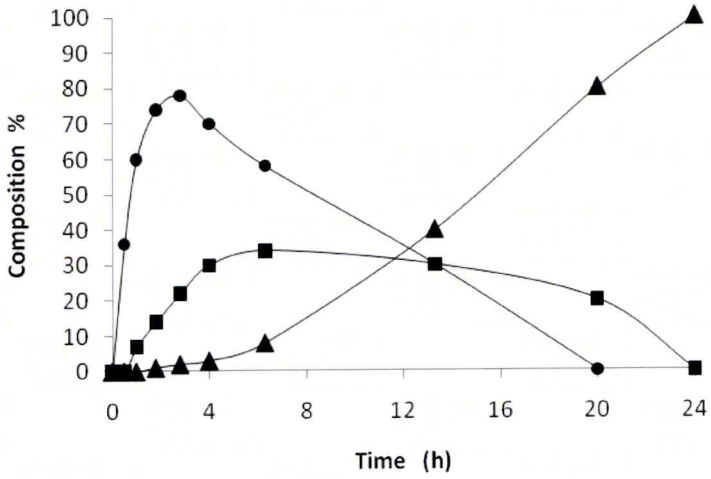
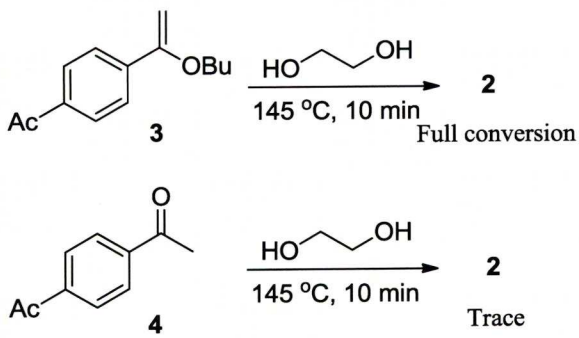


Figure 3.02. Composition (%) vs. time for enol ether **3** (●), mixed ketal **5** (■), cyclic ketal **2** (▲) in the reaction of **1** with BVE. Reaction conditions: $Pd(OAc)_2$ (0.25 mol%), dppp (0.5 mol%), **1** (3 mmol), BVE (9 mmol), NEt_3 (9 mmol) in 6 mL ethylene glycol at 145 °C.

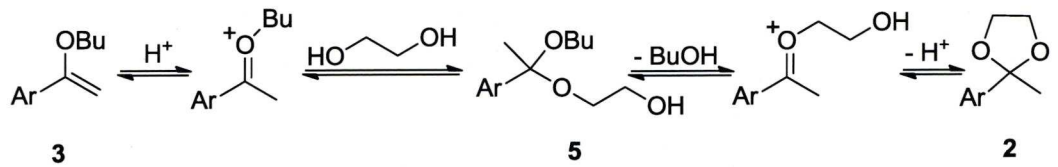
Further evidence for this pathway comes from observing the reactions of **3** and **4** with ethylene glycol in the absence of base (Scheme 3.14). Whilst complete conversion of **3** to **2** took less than ten minutes, **4** produced only a trace (tlc) of the ketalised product under the same conditions. If the reaction were to go by the hydrolysis-ketalisation sequence the reaction of **4** would be as fast as, if not faster than, that of **3**.



Scheme 3.14. Ketalisation of enol ether **3** vs. ketone **4** in ethylene glycol

A possible mechanism is shown in Scheme 3.15. Protonation of **3** by $[HNEt_3]^+$ or by the ethylene glycol itself generates an oxocarbenium ion[15, 31, 35] that undergoes nucleophillic attack by ethylene glycol, and subsequent loss of a proton

leads to the isolable mixed ketal **5**. Protonation of **5** followed by elimination of butanol gives a new oxocarbenium, an intermediate that the current reaction has in common with Heck/cyclisation procedures that employ hydroxyl alkyl vinyl ethers. Neighbouring group participation assists the elimination and stabilises the tertiary carbocation. Finally, an intramolecular nucleophillic attack by the pendant hydroxyl function and loss of a proton release the final product **2**.



Scheme 3.15. Proposed mechanism for the conversion of **3** to **2** in ethylene glycol

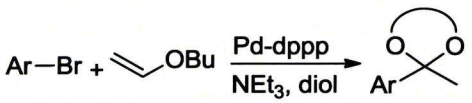
We have previously noted that the ketals undergo exchange with the ethylene glycol solvent under the Heck reaction conditions,[34] a reaction likely to proceed via oxocarbenium and mixed ketal intermediates, adding weight to our suggested mechanism. A Spartan calculation reveals that the highest HOMO density of **3** locates at the terminal carbon of the C=C double bond. Protonation at that carbon is therefore expected to take place easily, affording the oxocarbenium intermediate suggested.

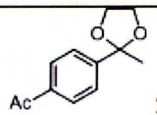
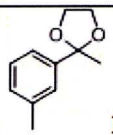
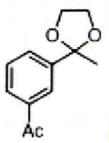
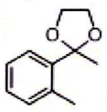
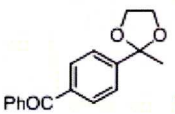
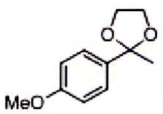
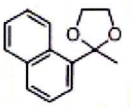
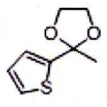
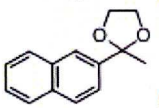
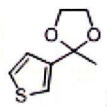
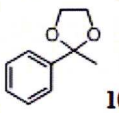
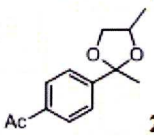
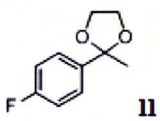
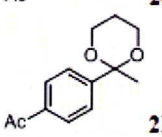
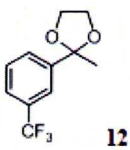
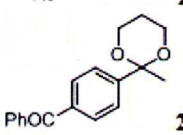
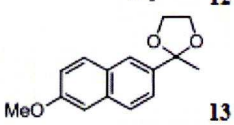
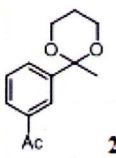
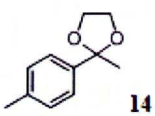
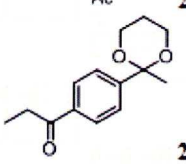
Before exploring the scope of the catalysis for the synthesis of ketals, we undertook a limited screening using the coupling of **1** with BVE in ethylene glycol as a model reaction (Scheme 3.12). The results show that the catalyst loading could be reduced to as low as 0.1 mol%, without sacrificing yield. The temperature had to remain high in order to keep reasonable reaction times, however. Thus, at 80 °C the conversion to **2** was only 20% in 72 h. With these observations, we then turned our attention to the scope of the reaction with respect to the aryl bromides used. Other

diols were also considered, aiming to generate ketals other than dioxolanes. The results are presented in Table 3.01.

As can be seen, **1** reacted with BVE in ethylene glycol, affording the 5-membered ketal **2** in a good yield of 82% (entry 1). In fact, a wide range of aryl groups can be tolerated, including electron deficient (entries 1-8), electron rich (entries 9-13), and sterically demanding (entry 12). Heterocyclic aryl bromides also reacted to yield the cyclic ketals in good yields (entries 14-15). Of particular interest is that the compounds **2**, **6** and **7** were obtained from aryl bromides that contain a carbonyl group, exhibiting excellent chemoselectivity with no di-ketalised product detected. When the solvent was changed from ethylene glycol to 1,2-propanediol, we were pleased to see that the substituted ketal **20** was produced, interestingly with some diastereoselectivity (60:40). An attempt to increase this selectivity by lowering the temperature to 80 °C once the Heck reaction had finished was not successful; the d.r. remained at 60:40 and a yield of only 22% was obtained in 72 h. Of further interest is that when the Heck reaction was carried out in 1,3-propanediol, 6-membered dioxanes, including carbonyl-containing ones, were produced by reacting the appropriate aryl bromide, again in decent yields (entries 17-20). Although the protocol developed thus far was tolerant of a range of bromides and alcohols, some compounds were not obtainable by this method. For example, 3-chloro-1,2-propanediol was unable to act as a solvent for the reaction; the Heck reaction did not proceed and the starting aryl bromide was recovered. Some other alcohols also proved problematic, 2-methyl-1,3-propanediol and glycerol being examples where either no desired product was obtained or sluggish reactions occurred.

Table 3.01 Heck arylation of BVE with aryl bromides in diols leading to ketals[a]

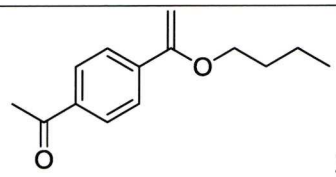
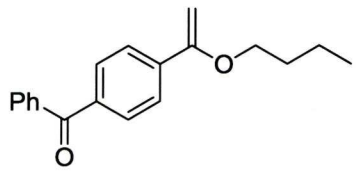
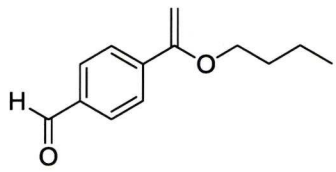


Entry	Product	Yield[b]	Entry	Product	Yield[b]
1	 **2**	82	11	 **15**	71
2	 **6**	75	12	 **16**	73
3	 **7**	80	13	 **17**	76
4	 **8**	73	14	 **18**	70
5	 **9**	66	15	 **19**	73
6	 **10**	77	16	 **20**	78[c]
7	 **11**	74	17	 **21**	72
8	 **12**	72	18	 **22**	80
9	 **13**	74	19	 **23**	73
10	 **14**	75	20	 **24**	78

[a] Reaction conditions: $Pd(OAc)_2$ (0.1 mol%), dppp (0.2 mol%), ArBr (3 mmol), BVE (3 mmol), NEt_3 (9 mmol), 145 °C, 24-36 h.
[b] Yields given are for isolated products
[c] dr = 60:40 determined by ^1H NMR.

Enol ethers such as 2-methoxy propene react with diols to form ketals as a means of diol protection and the reaction is promoted by Brønsted acids, typically *p*-toluene sufonic acid.[47, 48] This, in conjunction with our suggested acid-catalyzed mechanism for cyclisation, led us to investigate whether we could overcome these difficulties with an acid-catalysed cyclisation of isolated enol ethers. Hopefully this would also allow us to produce cyclic ketals from enol ethers under mild conditions. It was, therefore, necessary to isolate the enol ethers originally produced in the Heck reaction. As the Heck reaction was fast at 145 °C and ketal formation began shortly afterwards, an adjustment to the conditions was necessary in order to maximise the yield of the enol ether. Quickly we found that by dropping the reaction temperature to 100 °C, the formation of **5** and **2** from **1** and BVE were minimal whilst the Heck reaction remained fast. We also found that simple extraction with diethyl ether was sufficient to remove the arylated enol ether product **3** from the ethylene glycol without too much of the solvent being removed alongside it. Following this, a rapid column chromatography with a basified eluant allowed for isolation of **3** in 85% yield on a multi-gram scale. This further demonstrates the versatility of the Heck reaction of electron-rich olefins in this solvent, adding a new product that is available in excellent yield from the same reaction components, depending on the reaction and/or work up conditions. The results for selected aryl bromides are shown in Table 3.02.

Table 3.02. Isolation of arylated enol ethers from the Heck in ethylene glycol[a]

Entry	Product	Time/ h	Yield[b]
1	 **3**	2	85
2	 **25**	3	90
3	 **26**	3	75

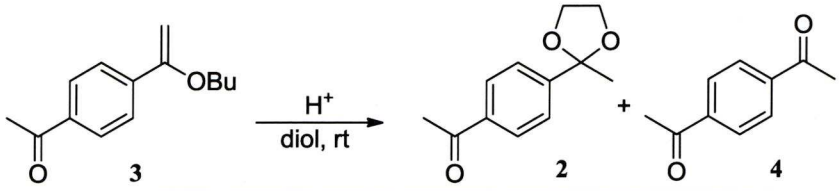
[a] Reaction conditions: $Pd(OAc)_2$ (1 mol%), dppp (2 mol%), ArBr (25 mmol), BVE (60 mmol), NEt_3 (60 mmol), 100 °C.
[b] Yields given are for isolated products.

In ketalisation of enol ethers with diols to protect the diols, an excess of the enol ether is usually used. As a consequence, acidic hydrolysis of the enol ether to the corresponding ketone is not a particularly big problem. Given the reverse of this is true for the reaction under question, a protocol that minimises the hydrolysis of the enol ether was required. A variety of acids were therefore tried using ethylene glycol as both the ketalisation reagent and solvent. The results are shown in Table 3.03.

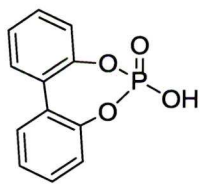
As can be seen, different acids produced varying levels of success in terms of conversion and selectivity. Although full conversion could be achieved in almost instantaneous reactions with the strong acids in entries 1-5, the isolated yields of **2** were low due to high levels of hydrolysis to give **4**, even when care was taken to dry the diol and substrate. Acetic acid (pKa = 4.8) produced a very slow reaction, with only trace quantities of the ketal and hydrolysis product being obtained (entry 6).

Other weak organic acids (entries7-8) (pKa = 4.2, 3.44, respectively) were not successful either for these reactions, giving only trace conversions to the ketal. The enol ether remained intact and only very small amounts of the hydrolysis product were detectable by tlc after 10 minutes. It is believed that a mixture of low solubility and insufficient acidity prevents these acids from successfully promoting the reaction.

Table 3.03. Effect of various acids on ketalisation of **3**[a]



3 **2** **4**

Entry	Acid	Time/min	Conversion	Yield[b] **2**	**4**
1	HBF_4	2	100	55	30
2	TfOH	2	100	50	25
3	HCl[c]	2	100	58	32
4	H_2SO_4	2	100	45	36
5	HNO_3	2	100	50	34
6	CH_3COOH	10	10	Trace	Trace
7	$PhCO_2H$	10	<5	-	-
8	*p*-NO_2PhCO_2H	10	<5	-	-
9		2	100	74	<5

[a] Reaction conditions: 0.25 mmol **3,** 2% acid in ethylene glycol.
[b] Isolated yields [c] 4 M solution in dioxane

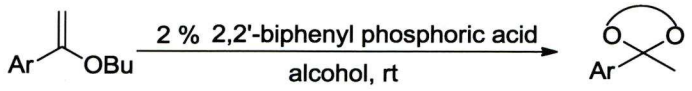
The phosphoric acid in entry 9 (pKa ~1.3)[49] gave a significantly better yield for **2** than the other acids tried, whilst retaining high activity. This relatively strong acid is easy to handle and dry, and is easily available. The acid allowed for a mild, catalytic and high-yielding protocol for the production of **2** from **3**. In addition to the

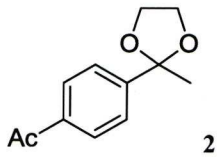
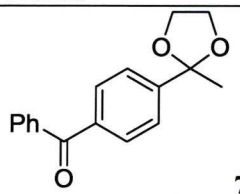
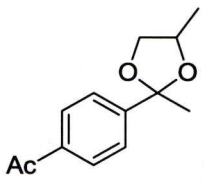
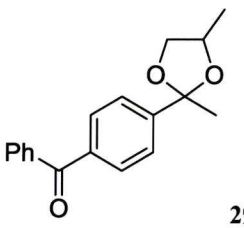
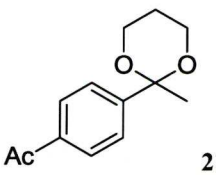
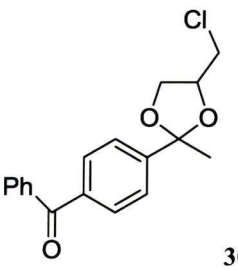
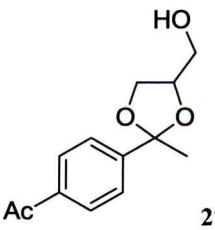
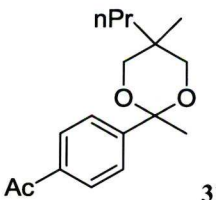
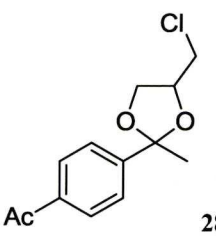
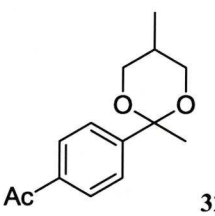
favourable conditions, the reaction was completely selective for the enol ether and no trace of the diketalised product was detected.

With an effective set of conditions established, we decided to expand the scope of the reaction to include functionalised diols and other carbonyl-containing enol ethers. The results are shown in Table 3.04. Both acetyl and benzoyl-containing enol ethers are viable substrates, reacting with a range of diols to produce the respective ketals. Thus, ethylene glycol, propylene glycol, 1,2-propane diol, 3-chloro-1,2-propanediol and glycerol reacted with **3**, most being complete in short reaction times with very good yields. As aforementioned, some of these diols did not enter the ketalisation under the in situ Heck conditions.

The carbonyl group in the products can undergo further reactions, and of particular interest is that the ketals **27**, **28** and **31** provide additional sites for functionalisation. However, when the formyl-substituted enol ether **26** was reacted with ethylene glycol, the reaction was not selective, affording a mixture of products in which the formyl group was always acetalised.

Table 3.04. Acid-catalysed ketalisation of enol ethers[a]



Entry	Product	Yield[b]	Entry	Product	Yield[b]
1	 **2**	74	6	 **7**	76
2	 **19**	75[c]	7	 **29**	75[c]
3	 **21**	70	8	 **30**	77[c]
4	 **27**	80[d]	9	 **31**	75[e]
5	 **28**	78	10	 **32**	79

[a] Reaction Conditions: 1 mmol enol ether, 2 mol % phosphoric acid, alcohol, 2-60 min
[b] Isolated yields[c] d.r. = 60:40[d] d.r. = 70:30 [e] Reaction conducted in the molten diol at 60 °C

The carbonyl group in the products can undergo further reactions, and of particular interest is that the ketals **27**, **28** and **31** provide additional sites for functionalisation. However, when the formyl-substituted enol ether **26** was reacted with ethylene glycol, the reaction was not selective, affording a mixture of products in which the formyl group was always acetalised.

3.3 Conclusions and Future Work

In conclusion, we have developed a simple, chemoselective and efficient procedure for the production of cyclic ketals from aryl bromides via a regioselective Heck reaction of butyl vinyl ether in alcohol solvents. Following the Heck arylation, ketalisation of the resulting arylated enol ether with the solvent takes place, leading to a variety of cyclic ketals. The method negates the use of more expensive hydroxy alkyl vinyl ethers and allows both 5- and 6-membered ketals containing sensitive functional groups to be prepared. Evidence shows that the reaction proceeds via a mixed ketal intermediate and not by hydrolysis to the corresponding ketone and subsequent ketalisation. Further optimisation identified a phosphoric acid, which is capable of catalysing the ketalisation of isolated enol ethers with problematic diols under mild conditions. Particularly noteworthy are some of the compounds found in Table 3.04, as they have a synthetic handle on the ketal ring in the form of C-Cl or –OH bonds. Their similarity to intermediates in the synthesis of B-12 highlights that this method is a viable alternative for the synthesis of bioactive ketals, particularly when chemoselectivity is a concern.

Future work would be to develop the reaction so that the problematic alcohols could be used for ketalisation in a one-pot procedure. This could be achieved either by exploiting the exchange observed between solvent and cyclic ketal or by finding

conditions that allow the Heck reaction to take place in these alcohols as solvent. The substrate scope could be extended to include real synthetic examples on more advanced intermediates. Also, examples of aryl bromides containing acid-labile groups such as Boc-protected nitrogen groups would demonstrate the usefulness of the basic environment.

The stable yet reactive nature of the enol-ethers produced by the Heck reaction of electron-rich olefins has not yet been fully exploited. As yet, only oxygen nucleophiles have been employed in one-pot transformations. Extending the range of nucleophiles to add to the oxocarbenium ions generated upon protonation of the enol-ether would open up a plethora of compounds available from this chemistry.

3.4 Experimental

Preparation of catalyst stock solution

An oven-dried, two-necked round bottom flask was charged with $Pd(OAc)_2$ (7 mg, 0.03 mmol), dppp (25 mg, 0.06 mmol) and 10 mL ethylene glycol. The flask was evacuated and back-filled with N_2 for three times and the solution stirred at room temperature for 3 h, at which time a homogeneous, bright yellow solution was obtained. The stock solution was kept under a slight pressure of N_2 and used immediately.

General procedure for the Heck reaction of aryl bromides with BVE in alcohol solvents to form aryl substituted cyclic ketals

An oven-dried Schlenk tube was charged with 4-bromoacetophenone **1** (597 mg, 3 mmol) and ethylene glycol (5 mL). The flask was evacuated and backfilled with nitrogen for three times. NEt_3 (1.2 mL, 9 mmol) and 1 mL of the Pd-dppp stock

solution (0.003 mmol, 0.1 mol% Pd) were added via a syringe and the tube placed in a parallel reactor (block temperature 145 °C). The mixture was vigorously stirred for 2-3 mins after which time BVE (1.1 mL, 9 mmol) was injected and the reaction monitored by tlc until no trace of **1** or **5** remained. The flask was cooled to room temperature and water (30 mL) was added. The aqueous layer was then extracted with Et_2O (3 x 20 mL) and the combined organic layers washed with H_2O (20 mL). The solvent was removed *in vacuo* and the crude residue purified by flash chromatography on silica gel (hexanes-ethyl acetate, 95:5) to give 1-(4-(2-methyl-1,3-dioxolan-2-yl)phenyl)ethanone **2** in 82% yield.

General procedure for the Heck reaction of aryl bromides with BVE in alcohol solvents to form aryl substituted enol ethers

An oven dried, two-necked round bottom flask fitted with a reflux condenser was charged with $Pd(OAc)_2$ (56 mg, 0.25 mmol), dppp (205 mg, 0.50 mmmol), 4-bromoacetophenone (5.05 g, 25 mmol) and 40 mL ethylene glycol. The flask was evacuated and back filled with nitrogen for three times and NEt_3 (9.6 mL, 75 mmol) was added via a syringe. The flask was added to an oil bath at 100 °C and stirred vigorously for 3-4 mins until a bright yellow colour developed, at which point BVE (8 mL, 75 mmol) was added via a syringe. After an appropriate time (1-3 h), the reaction was cooled and the crude reaction mixture was extracted with Et_2O (3 x 100 mL). The combined extracts were concentrated in vacuo and the crude residue was purified by flash chromatography (hexanes-EtOAc-NEt_3, 98:1:1) to give 4.63 g 1-(4-(1-butoxyvinyl)phenyl)ethanone (85%).

General procedure for the acid-catalysed conversion of enol ethers to cyclic ketals in alcohol solvents.

An oven-dried, two-necked round bottom flask was charged with **3** (218 mg, 1 mmol), phosphoric acid (2 mg, 0.02 mmol) and ethylene glycol (2 mL). The flask was sealed and stirred for an appropriate time until consumption of the starting material was confirmed by tlc. NEt_3 (0.1 mL, 1 mmol) was added and the mixture extracted with Et_2O (3 x 15 mL), and rinsed with H_2O (2 x 10 mL). The combined organic extracts were concentrated *in vacuo* and the resulting crude residue purified by flash chromatography (Hexanes-EtOAc, 97:3) to give 152 mg of **2** (74%).

3.5 Compounds characterised

1-(4-(2-Methyl-1,3-dioxolan-2-yl)phenyl)ethanone 2

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.4 Hz, 2 H), 7.58 (d, *J* = 8.4 Hz, 2 H), 4.10-4.01 (m, 2 H), 3.81-3.75 (m, 2 H), 2.61 (s, 3 H), 1.66 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.2, 148.9, 137.1, 128.8, 126.0, 108.9, 64.98, 27.8, 27.1.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{12}H_{15}O_3$: 207.1021; found: 207.1026.

Anal Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.20; H, 6.87.

1-(4-(1-Butoxyvinyl)phenyl)ethanone 3

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91(d, *J* = 8.8 Hz, 2 H), 7.70 (d, *J* = 8.8 Hz, 2 H), 4.76 (d, *J* = 2.8 Hz, 1 H), 4.76 (d, *J* = 2.8 Hz, 1 H), 3.86 (t, *J* = 6.4, Hz, 2 H), 1.90-1.73 (m, 2 H), 2.59 (s, 3 H) 1.65-1.46 (m, 2 H), 0.99 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.1, 159.2, 141.4, 137.1, 128.6, 125.7, 84.6, 68.1, 31.5, 27.1, 19.8, 14.1.

1-(4-(1-Butoxy-1-(2-hydroxyethoxy)ethyl)phenyl)ethanone 5

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.4 Hz, 2 H), 7.61 (d, *J* = 8.4 Hz, 2 H), 3.82-3.74 (m, 2 H), 3.59-3.52 (m, 1 H), 3.52-3.44 (m, 1 H), 3.44-3.36 (m, 1H), 3.35-3.29 (m, 1 H), 2.61 (s, 3 H), 1.69-1.55 (m, 2 H), 1.59 (s, 3 H), 1.47-1.36 (m, 2 H), 0.94 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.4, 148.9, 136.8, 128.6, 126.9, 101.4, 63.2, 62.5, 61.6, 32.3, 27.2, 27.0, 20.1, 14.3.

HRMS – ES: m/z $[M + Na]^+$ Calcd for $C_{16}H_{24}O_4Na$: 303.1572; found: 303.1558.

1-(3-(2-Methyl-1,3-dioxolan-2-yl)phenyl)ethanone 6

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (t, *J* = 1.6, 1 H), 7.90 (dt, *J* = 8.0, 1.4 Hz, 1H), 7.68 (dt, *J* = 8.0, 1.4 Hz, 1H), 7.45 (t, 7.6 Hz, 1H),), 4.15-4.02 (m, 2 H), 3.85-3.75 (m, 2 H), 2.65 (s, 3 H), 1.66 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.4, 144.6, 137.6, 130.5, 129.0, 128.2, 125.6, 108.9, 65.0, 28.0, 27.1.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{12}H_{15}O_3$: 207.1021; found: 207.1022.

Anal Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.80; H, 6.82.

(4-(2-methyl-1,3-dioxolan-2-yl)phenyl)(phenyl)methanone 7

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85-7.77 (m, 4 H), 7.65-7.56 (m, 3 H), 7.52-7.45 (m, 2 H), 4.12-4.05 (m, 2 H), 3.86-3.77 (m, 2 H), 1.69 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.8, 148.3, 138.0, 137.6, 132.9, 130.7, 130.5, 128.7, 126.0, 109.0, 65.1, 27.9.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{17}H_{17}O_3$: 269.1177; found: 269.1176

Anal Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.17; H, 6.04.

2-Methyl-2-(naphthalen-1-yl)-1,3-dioxolane 8

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 9.0 Hz, 1H), 7.72–7.64 (m, 3 H), 7.40–7.27 (m, 3 H), 3.97–3.93 (m, 2 H), 3.68–3.65 (m, 2 H), 1.78 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.4, 133.5, 129.3, 128.0, 127.6, 125.3, 124.7, 124.3, 123.8, 122.6, 108.6, 61.2, 26.5.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{14}H_{15}O_2$: 215.1072; found: 215.1075.

Anal Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.61. Found: C, 78.55; H, 6.65.

2-methyl-2-(naphthalen-2-yl)-1,3-dioxolane 9

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (s, 1 H), 7.88-7.80 (m, 3 H), 7.58 (dd, , J = 8.0, 1.6 Hz, 1H), 7.51-7.45 (m, 2H),), 4.14-4.02 (m, 2 H), 3.86-3.78 (m, 2 H), 1.74 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.0 133.4(4), 133.4(2), 128.7, 128.6, 128.0, 126.6, 126.5, 124.4, 124.1, 109.4, 65.0, 28.0.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{14}H_{15}O_2$: 215.1072; found: 215.1071.

Anal Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.61. Found: C, 78.61; H, 6.62.

2-Methyl-2-phenyl-1,3-dioxolane 10

1H NMR (400 MHz, $CDCl_3$) δ = 7.49-7.47 (m, 2H), 7.35-7.27 (m, 3H), 4.03-3.99 (m, 2H), 3.76-3.73 (m, 2H), and 1.65 (s, 3H).

13C NMR (100 MHz, CDCl3) δ = 143.8, 128.7, 128.2, 125.7, 109.2,

64.8, 28.1

HRMS Calcd for $C_{10}H_{13}O_2$ (M + H)+: 165.0916. Found: 165.0917

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H,7.37. Found: C, 72.95; H, 7.34.

2-(4-Fluorophenyl)-2-methyl-1,3-dioxolane 11

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.34 (m, 2 H), 6.96-6.89 (m, 2 H), 3.99-3.90 (m, 2 H), 3.72-3.63 (m, 2 H), 1.55 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8 (d, $J_{C\text{-}F}$ = 244 Hz), 139.6 (d, $J_{C\text{-}F}$ = 3 Hz), 127.5 (d, $J_{C\text{-}F}$ = 8 Hz), 115.4 (d, $J_{C\text{-}F}$ = 21 Hz), 108.9, 64.8, 28.1

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{10}H_{12}FO_2$: 183.0821; found: 183.0824.

Anal Calcd for $C_{10}H_{11}FO_2$: C, 65.92; H, 6.09. Found: C, 66.11; H, 6.12.

2-(6-Methoxynaphthalen-2-yl)-2-methyl-1,3-dioxolane 13

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (s, 1 H), 7.85-7.68 (m, 2 H), 7.65-7.51 (m, 1 H), 7.25-7.11 (m, 2 H), 4.25-4.05 (m, 2 H), 3.92 (s, 3 H), 3.91-3.79 (m, 2 H), 1.73 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 138.8, 134.6, 130.1, 128.8, 127.3, 124.6, 124.3, 119.3, 109.4, 106.0, 64.9, 55.7, 28.0.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{15}H_{16}O_3$: 245.1099; found: 245.1101.

Anal Calcd for $C_{15}H_{15}O_3$: C, 73.75; H, 6.60. Found: C, 73.93; H, 6.66.

2-Methyl-2-p-tolyl-1,3-dioxolane 14

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, J = 7.6 Hz, 2 H), 7.16 (d, J = 7.6 Hz, 2 H), 4.08-3.95 (m, 2 H), 3.82-3.72 (m, 2 H), 2.34 (s, 3 H), 1.65 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.8, 137.9, 129.3, 125.6, 109.3, 64.8, 28.1, 21.5.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{11}H_{15}O_2$: 179.1067; found: 179.1070.

Anal Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.29; H, 7.96.

2-Methyl-2-m-tolyl-1,3-dioxolane 15

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57-7.53 (m, 2 H), 7.25-7.12 (m, 2 H), 4.05-3.95 (m, 2 H), 3.77-3.65 (m, 2 H), 2.50 (s, 3 H), 1.68 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.0, 136.0, 132.3, 128.3, 126.5, 126.0, 109.9, 64.4, 26.7, 21.1.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{11}H_{15}O_2$: 179.1067; found: 179.1064.

Anal Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.30; H, 7.97.

2-Methyl-2-o-tolyl-1,3-dioxolane 16

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48-7.19 (m, 3 H), 7.18-7.09 (m, 1H), 4.18-4.03 (m, 2 H), 3.92-3.73 (m, 2 H), 2.36 (s, 3 H), 1.66 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 138.2, 129.0, 128.5, 126.3, 122.7, 109.3, 64.8, 28.1, 21.9.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{11}H_{15}O_2$: 179.1067; found: 179.1068.

Anal Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.38; H, 7.98.

2-(4-Methoxyphenyl)-2-methyl-1,3-dioxolane 17

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 4.10-3.95 (m, 2 H), 3.87-3.76 (m, 2 H), 3.81 (s, 3 H), 1.70 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6, 135.9, 126.9, 113.9, 109.2, 64.8, 55.7, 28.1.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{11}H_{15}O_3$: 195.1016; found 195.1016.

Anal Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.17; H, 7.30.

2-Methyl-2-(thiophen-3-yl)-1,3-dioxolane 19

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30-7.24 (m, 2 H), 7.07 (dd, *J* = 4.8, 1.6 Hz, 1 H), 4.10-3.98 (m, 2 H), 3.92-3.87 (m, 2 H), 1.68 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.6, 126.4, 126.2, 121.8, 107.8, 65.1, 27.4.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{11}H_{15}O_3$:171.0474; found 171.0474

Anal Calcd for $C_8H_{11}O_2S$: C, 56.44; H, 5.94. Found: C,56.56; H,6.00.

1-(4-(2,4-Dimethyl-1,3-dioxolan-2-yl)phenyl)ethanone 20

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.4 Hz, 2H). 7.61 (d, J = 8.0 Hz, 1.2 H), 7.58 (d, 8.0 Hz, 0.8 H), 4.5-4.34 (m, 0.6 H), 4.17 (dd, J= 8.0, 6.0 Hz, 0.6 H), 4.11-3.97 (m, 0.4 H), 3.88 (t, J = 6.8 Hz, 0.4 H), 3.65-3.54 (m, 0.4 H), 3.27 (t, J = 8.0 Hz, 0.6 H), 2.61 (s, 3 H), 1.66 (s, 1.2 H), 1.63 (s, 1.8 Hz), 1.34 (d, J = 6.0 Hz, 1.2 H), 1.19 (d, J = 6.0 Hz, 1.8 H). Product exists as a mixture of diastereoisomers with d.r. = 60:40

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.3, 150.3, 149.5, 137.0, 136.9, 128.9, 128.8, 128.7, 128.6, 128.9, 125.8, 109.0, 73.7, 72.5, 71.6, 71.3, 28.6, 28.5, 19.2, 18.7.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{11}H_{15}O_2$: 221.1178; found: 221.1172.

Anal Calcd for $C_{11}H_{14}O_2$: C, 70.89; H, 7.32. Found: C, 71.03; H, 7.37.

1-(4-(2-Methyl-1,3-dioxan-2-yl)phenyl)ethanone 21

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, 8.0 Hz, 2 H), 7.55 (d, *J* = 8.0 Hz, 2 H), 3.94-3.88 (m, 2 H), 3.75 (td, *J* = 12.0, 2.6 Hz, 2 H), 2.63 (s, 3 H), 2.14 (qt, *J* = 12.6, 5.0 Hz, 1H), 1.52 (s, 3 H), 1.31-1.24 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.2, 147.2, 137.0, 129.3, 127.5, 100.7, 61.8, 32.4, 27.1, 25.7.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{13}H_{17}O_3$: 221.1178; found: 221.1179.

Anal Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.97; H, 7.34.

(4-(2-Methyl-1,3-dioxan-2-yl)phenyl)(phenyl)methanone 22

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91-7.82 (m, 4 H), 7.65-7.56 (m, 3 H), 7.54-7.47 (m, 2 H), 3.98-3.89 (m, 2 H), 3.80 (td, *J* = 11.1, 2.5 Hz, 2 H), 2.22-2.08 (m, 1 H), 1.56 (s, 3 H), 1.34-1.25 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.5, 144.3, 135.7, 135.2, 130.6, 128.8, 128.2, 126.5, 125.0, 98.6, 59.6, 30.2, 23.5.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{18}H_{19}O_3$: 283.1329; found: 283.1330.

Anal Calcd for $C_{18}H_{19}O_2$: C, 76.57; H, 6.43. Found: C, 76.67; H, 6.49.

1-(3-(2-Methyl-1,3-dioxan-2-yl)phenyl)ethanone 23

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (t, *J* = 1.8 Hz, 1 H), 7.92 (dt, *J* = 7.6, 1.4 Hz, 1 H), 7.66 (dt, *J* = 7.6, 1.4 Hz, 1 H), 7.52 (t, *J* = 7.6 Hz, 1 H), 3.98-3.88, (m, 2 H), 3.75 (dt, *J* = 12.0, 2.4 Hz, 1 H), 2.64 (s, 3 H), 2.24-2.07 (m, 1 H), 1.53 (s, 3 H), 1.36-1.24 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.8, 142.9, 138.6, 132.3, 129.9, 128.4, 127.4, 100.9, 62.0, 32.9, 27.5, 26.1.

HRMS – EI: m/z $[M + H]^+$ Calcd for Calcd for $C_{13}H_{17}O_3$: 221.1172. found: 221.1175.

Anal Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.10; H, 7.40.

1-(4-(2-Methyl-1,3-dioxan-2-yl)phenyl)propan-1-one 24

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, 8.4 Hz, 2 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 3.98-3.86 (m, 2 H), 3.76 (td, *J* = 12.4, 2.8 Hz, 2H), 3.02 (q, *J* = 7.2 Hz, 2 H), 2.13 (qt, *J* = 12.8, 5.2 Hz, 1 H), 1.51 (s, 3 H), 1.35-1.24 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.9, 147.0, 136.8, 128.9, 127.5, 100.7, 61.9, 32.4, 32.3, 25.7, 8.7.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{14}H_{19}O_3$: 235.1329; found: 235.1327.

Anal Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.95; H, 7.76.

(4-(1-Butoxyvinyl)phenyl)(phenyl)methanone 25

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11-7.71(m, 6 H), 7.70-7.56 (m, 1 H), 7.54-7.42 (m, 2H), 4.80 (d, *J* = 2.8 Hz, 1 H), 4.34 (d, *J* = 2.8 Hz, 1 H), 3.91 (t, *J* = 6.4 Hz, 2 H), 2.00-1.78 (m, 2 H), 1.68-1.48 (m, 2 H), 1.05 (t, *J* = 7.5 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.2, 166.3, 141.6, 138.0,134.0, 133.6, 132.8, 130.5, 130.1, 129.9, 85.6, 68.8, 31.7, 20.1, 14.3.

4-(1-Butoxyvinyl)benzaldehyde 26

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.00 (s, 1 H), 7.85 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H), 4.80 (d, *J* = 2.8 Hz, 1 H), 4.35 (d, *J* = 2.8 Hz, 1 H), 3.87 (t, *J* = 6.4 Hz, 2 H), 1.90-1.73 (m, 2 H), 1.66-1.49 (m, 2 H), 1.00 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.4, 159.1, 142.8, 136.4, 130.0, 126.2, 85.2, 68.1, 31.5, 19.9, 14.0.

1-(4-(4-(Hydroxymethyl)-2-methyl-1,3-dioxolan-2-yl)phenyl)ethanone 27

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.4 Hz, 2 H), 7.67-7.56 (m, 2 H), 4.20 (dd, *J* = 8.4, 6.4 Hz, 0.3 H), 4.17-4.04 (m. 0.3 H), 4.12-4.09 (m, 0.7 H), 3.90 (dd, *J* = 8.0. 5.2 Hz, 0.7 H), 3.87-3.74 (m, 1.4 H), 3.74-3.58 (m, 1 H), 3.57-3.43 (m, 0.6 H), 2.61 (s, 3 H), 1.68 (s, 2.1 H), 1.65 (s, 0.9 H). Product exists as a mixture of diastereoisomers with d.r. = 70:30

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.2, 149.6, 148.6, 137.2, 129.0, 128.9, 126.0, 125.6, 109.7, 77.9, 76.6, 66.8, 66.2, 63.7, 63.1, 28.3, 28.2(8), 27.1.

125HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{13}H_{17}O_4$: 237.1121; found: 237.1118.

Anal Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 68.93; H, 6.84.

1-(4-(4-(Chloromethyl)-2-methyl-1,3-dioxolan-2-yl)phenyl)ethanone 28

^1H NMR (400 MHz, $CDCl_3$): δ = 7.92-7.85 (m, 2 H), 7.53-7.43 (m, 2 H), 4.46-4.35 (m, 0.45 H), 4.22 (dd, *J* = 8.8, 6.0 Hz, 0.45 Hz), 4.20-4.10 (m, 0.55 H), 3.90 (dd, *J* = 4.8, 4.0 Hz, 0.55 H), 3.71 (dd, *J* = 8.8, 6.8 Hz, 0.55 H), 3.69-3.55 (m, 1 H), 3.54-3.41 (m, 1 H), 3.10 (dd, *J* = 11.2, 8.0 Hz, 0.45 H), 2.54 (s, 3 H), 1.60 (s, 1.65 H), 1.56 (s, 1.35 H). Product exists as a mixture of diastereoisomers with d.r. = 55:45

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.7, 147.9, 147.0, 135.8, 127.5, 127.4, 124.5, 124.3, 108.8, 75.3, 74.4, 67.6, 66.4, 43.6, 43.1, 27.0, 25.7.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{13}H_{16}ClO_3$: 255.0787; found: 255.0789.

Anal Calcd for $C_{13}H_{15}ClO_3$: C, 61.30; H, 5.94. Found: C, 61.40; H, 5.96.

(4-(2,4-Dimethyl-1,3-dioxolan-2-yl)phenyl)(phenyl)methanone 29

^1H NMR (400 MHz, $CDCl_3$): δ = 7.80-7.66 (m, 4 H), 7.62-7.45 (m, 3 H), 7.45-7.35 (m, 2 H), 4.35-4.24 (m, 0.6 H), 4.17 (dd, *J* = 8.0, 5.6 Hz, 0.6 H), 4.02-3.92 (m, 0.4 H), 3.82 (dd, *J* = 7.6, 6.4 Hz, 0.4 H, 3.54-3.44 (m, 0.4 H), 3.30-3.18 (m, 0.6 H), 1.59 (s, 1.2 H), 1.56 (s, 1.8 H), 1.25 (d, *J* = 6.0 Hz, 1.2 H), 1.11 (d, *J* = 6.0 Hz, 1.8 H). Product exists as a mixture of diastereoisomers with d.r. = 60:40.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.8, 149.6, 148.9, 138.0, 137.9(9), 137.5, 137.4, 132.9, 132.8, 130.5, 130.4(3), 130.4(1), 128.7, 125.7, 125.6, 109.1, 73.7, 72.5, 71.6, 71.3, 28.7, 28.5, 19.3, 18.7.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{17}H_{24}O_3$: 283.1329; found: 283.1332.

Anal Calcd for $C_{11}H_{14}O_2$: C, 76.57; H, 6.43. Found: C, 76.60; H, 6.45.

(4-(4-(Chloromethyl)-2-methyl-1,3-dioxolan-2-yl)phenyl)(phenyl)methanone 30

^1H NMR (400 MHz, $CDCl_3$): δ = 7.93-7.77 (m, 4 H), 7.73-7.57 (m, 3 H), 7.57-7.46 (m, 2 H), 4.53-4.44 (m, 0.4 H), 4.31 (dd, *J* = 8.8, 6.4 Hz, 0.4 H), 4.28-4.20 (m, 0.6 H), 3.99 (dd, *J* = 8.4, 4.4 Hz, 0.6 H), 3.83 (dd, *J* = 8.4, 7.2 Hz, 0.6 H), 3.77-3.63 (m, 1 H), 3.62-3.44 (m, 1 H), 3.20 (dd, *J* = 10.8, 8.8 Hz, 0.4 H), 1.71 (s, 1.8 H), 1.67 (s, 1.2 H). Product exists as a mixture of diastereoisomers with d.r. = 60:40.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.9, 132.9, 130.6, 130.5, 128.7(3), 128.6(8), 125.6, 125.5, 75.9, 69.1, 67.9, 66.3, 45.0, 44.6, 28.5, 28.4, 15.7.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{18}H_{18}ClO_3$: 317.0939; found: 317.0939.

Anal Calcd for $C_{18}H_{17}ClO_3$: C, 68.25; H, 5.41. Found: C, 68.43; H, 5.42.

1-(4-(2,5-Dimethyl-5-propyl-1,3-dioxan-2-yl)phenyl)ethanone 31

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94-7.89 (m, 2H), 7.48-7.45 (m, 2H), 3.47 (d, *J* = 11.6 Hz, 1 H), 3.39 (d, *J* = 11.0 Hz, 1 H), 3.31 (d, *J* = 11.0 Hz, 1 H), 3.24 (d, *J* = 11.6 Hz, 1 H), 2.55 (s, 3 H), 1.68-1.59 (m, 1 H), 1.46 (s, 1.5 H), 1.45 (s, 1.5 H), 1.31-1.25 (m, 1 H), 1.19 (s, 1.5 H) 1.15-1.01 (m, 1 H), 0.92 (t, *J* = 7.2 Hz, 1.5 H), 0.82-0.75 (m, 1 H), 0.71 (t, *J* = 7.2 Hz, 1.5 H), 0.44 (s, 1.5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.2, 147.1, 147.0, 137.0, 129.2, 127.5, 100.6, 100.4, 71.7, 70.7 39.0, 37.0, 32.9(0), 32.8(6), 32.1, 31.9, 27.1, 20.2, 19.2, 17.3, 16.0, 15.3, 15.2.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{17}H_{24}O_3$: 277.1804; found: 277.1801.

1-(4-(2,5-Dimethyl-1,3-dioxan-2-yl)phenyl)ethanone 32

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06-7.97 (m, 2 H), 7.62-7.57 (m, 2 H), 3.95-3.86 (m, 1.2 H), 3.84-3.77 (m, 0.8 H), 3.66-3.54 (m, 1.2 H), 3.30-3.21 (m, 0.8 H), 2.63 (s, 1.2 H), 2.62 (s, 1.8 H), 2.23-2.12 (m, 0.4 H), 1.59-1.50 (m, 0.6 H), 1.54 (s, 1.8 H), 1.51 (s, 1.2 H), 1.28 (d, *J* = 6.8 Hz, 1.8 H), 0.57 (d, *J* = 6.8 Hz, 1.2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.2, 147.5, 147.0, 137.0, 129.3, 129.1, 127.6, 127.2, 100.4, 68.3, 66.9, 32.5, 30.8, 29.5, 29.1, 15.8, 12.7.

HRMS – EI: m/z $[M + H]^+$ Calcd for $C_{14}H_{19}O_3$: 235.1329. found: 235.1331.

Anal Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.82; H, 7.75.

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Chapter 4

Regioselective Heck Reactions of Unsaturated Alcohols for the Synthesis of Oxygen Heterocycles

4.1 Introduction

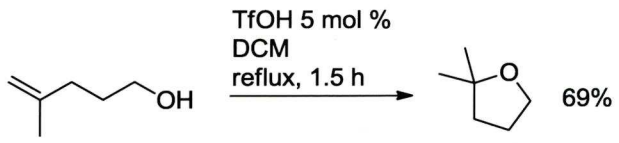
Saturated oxygen heterocylcles, such as tetrahydrofurans (THF's) and tetrahydropyrans (THP's), are extremely important compounds. They are found in the macrolide antibiotics and a great many natural products and bioactive compounds.[1-3] Many are being assessed for use in a diverse range of chemotherapeutic interventions. Because of their high importance a large number of procedures for the construction of saturated heterocylcles exist.[4-8] Still, they remain challenging targets and new methodologies will always draw attention from the synthetic community.

Electrophile Promoted Cyclisation of Unsaturated Alcohols

One of the most popular methods for the formation of heterocylcles is electrophile promoted cyclisation. This can occur in one of two ways. Firstly the electrophile acts as a catalyst (i.e. proton, metal ion) and is released after the reaction. Secondly, the electrophile is present in stoichiometric quantities and is incorporated into the final product (i.e. electrophillic halogen). For the purposes of this chapter, we will address the use of these types of reaction for formation of substituted THFs.

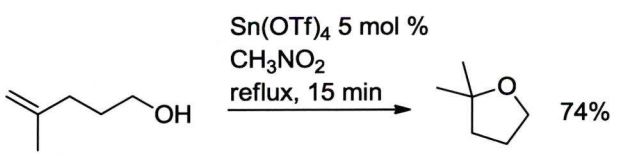
Although the Brønsted acid mediated cyclisation of unsaturated alcohols is well known, the acid-catalysed reaction is much less so and only a few examples can

be found in the literature.[9-11] Duñach and co-workers reported the triflic acid catalysed cyclisation of unsaturated alcohols.[12] Triflic acid was far superior to the other acids tried (H_2SO_4, CF_3COOH, H_3PO_4, *p*-TsOH.H_2O) and 5 mol % in DCM or CH_3NO_2 at reflux led to THFs or THPs in moderate to excellent yields (Scheme 4.01).



Scheme 4.01. Triflic acid catalysed cyclisation of an unsaturated alcohol

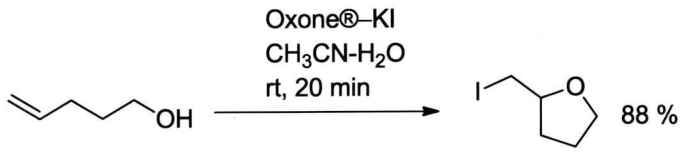
Only recently was the Lewis acid-catalysed intramolecular hydroalkoxylation reaction reported. Until a 2005 paper by Duñach, no Lewis acid catalyst had been reported for the reaction. They found $Sn(OTf)_4$ to be an efficient catalyst for the cyclisation of a variety of unsaturated alcohols.[13] 5 mol% of the catalyst allowed reactions to be completed in 10 min- 7 h in refluxing CH_3NO_2 (Scheme 4.02). Most of the alcohols tested were cyclised in excellent yield. Lanthanide triflate in an ionic liquid has also very recently been reported as a catalytic system for this reaction.[14]



Scheme 4.02. Lewis-acid catalysed cyclisation of an unsaturated alcohol

Electrophilic halogens are also a popular choice for promoting cyclisations of alkenes. Although the majority of reports are concerned with halolactonisation the corresponding haloetherification reactions have been reported.[15-17] The originally reported reaction utilised a $KI/I_2/NaHCO_3$ system,[18] one which is still popular

today.[19] However, most new methodologies deal with *in situ* generation of halogen from a halide source and an external oxidant,[20-23] avoiding the use hazards associated with the transport and storage.[24] A typical example is shown in Scheme 4.03.

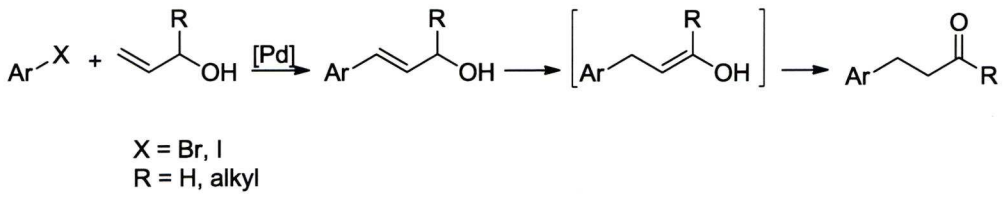


Scheme 4.03. A typical iodoetherification procedure

Heck Reactions of Unsaturated Alcohols

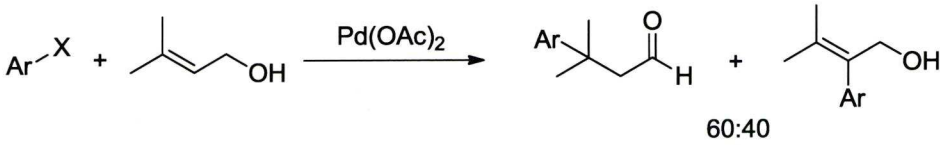
Initial investigations by Heck[25] and Magennis[26] on the Pd-catalysed Heck reaction of unsaturated alcohols revealed two prominent characteristics of these reactions-

1. The Heck reaction of unsaturated alcohols does not, in general, yield arylated unsaturated alcohols. Migration of the double bond by reversible addition of palladium hydride continues along the carbon chain until an enol intermediate is reached. Tautomerisation to the aldehyde or ketone results in the major products being aryl-substituted carbonyl compounds (Scheme 4.04). It was noted by the authors, however, that addition of a phosphine ligand (PPh_3) suppressed the isomerisation. With $Pd(OAc)_2$ and 3 eq PPh_3 the alcohol to carbonyl ratio was 4.2:1 (X= Br, R= CH_3, Ar = 2-MePh). $Pd(OAc)_2$ alone gave exclusively the carbonyl compound. The isomerisation is also stopped when a quaternary carbon centre exists between the olefin and the alcohol.



Scheme 4.04. Isomerisation of arylated unsaturated alcohols by Pd-H reinsertion

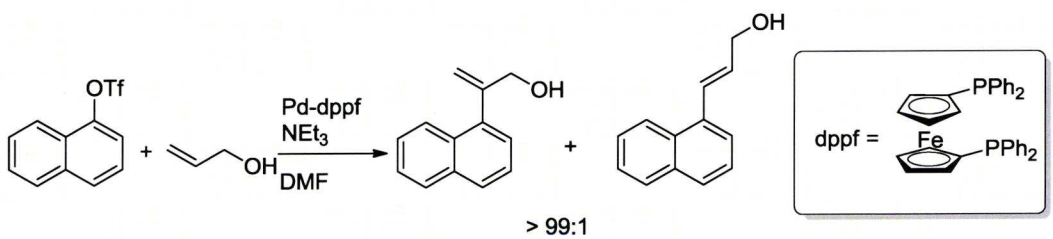
2. Using standard Heck conditions, arylation is strongly preferred at the terminal position of the olefinic bond. This preference is so strong that Heck reported the arylation of the allylic alcohol in Scheme 4.05 at the disubstituted terminal position was favoured 60:40 over the monosubstituted internal position. Arylation at the internal position led mainly to the alcohol product, presumably due to the stability of the tetrasubstituted olefin towards Pd-H addtition.



Scheme 4.05. β-Selectivity in Heck arylation of unsaturated alcohols

The preference for external substitution outlined in 2 above is true for the vast majority of reports on the Heck reaction of unsaturated alcohols.[27-37] However, the products of internal arylation are also desireable and serve as useful building blocks in the synthesis of natural products, antimalarials, anticancer and non-steroidal anti-inflammatory drugs such as the brufens.[38-42] Given this fact, it is important to develop methodologies to affect the internal arylation in high selectivity. Only a few reports exist where this has been achieved; the most successful are outlined below.

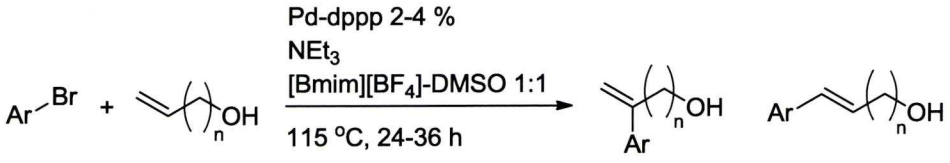
Cabri and co-workers were the first to realise high levels of selectivity for internal arylation of unsaturated alcohols.[43] Using aryl triflates and bidentate ligands such as dppp, dppf or dppb selectivity of <99:1 could be achived for internal arylation. Hence, the arylation of allyl alcohol in the presence of a Pd-dppf catalyst (2.5 mol%) proceeded with >99:1 internal selectivity (Scheme 4.06). A 90% yield of the substituted alcohol was obtained after 1 h reaction time at 100 °C in DMF. For allylic alcohols, dppf was required to obtain complete conversion. The formation of stable Pd(dppp)allyl complexes was implicated in the failure of dppp to achieve total consumption of the starting material. A homallylic alcohol was also successfully arylated using the Pd-dppp catalyst, albeit with a lower selectivity of 90:10. An attempt to switch from a triflate to an iodide led to a complex reaction mixture containing carbonyl compounds and alcohols resulting from both internal and external arylation.



Scheme 4.06. Pd-dppf for regioselective arylation of unsaturated alcohols

Work in this group revealed that ionic liquids were also useful solvents for regioselective internal arylation of unsaturated alcohols.[44] As was also found for enamides,[45] a mixture of [Bmim][BF_4]-DMSO was more successful than the pure ionic liquid (Scheme 4.07). Allyl alcohol was arylated exclusively at the internal position and good to excellent yields were obtained for a variety of aryl bromides. No isomerisation took place and the reactions yielded only the substituted alcohols. It is thought that the use of the chelating bisphosphine ligand is responsible for this

selectivity. Presumably it is more difficult for enough coordination sites to become available for efficient addition/reinsertion of the olefin and hydride. Homallylic and higher alcohols were also arylated in good to excellent yields, albeit with a reduced selectivity (internal 70-80%). Typical reaction conditions were 2-4 mol% $Pd(OAc)_2$, dppp (2 eq to Pd), NEt_3, [Bmim][BF_4]-DMSO 1:1, 115 °C, 24-36 h. This is the only report, to the best of our knowledge, for the general regioselective internal arylation of unsaturated alcohols.



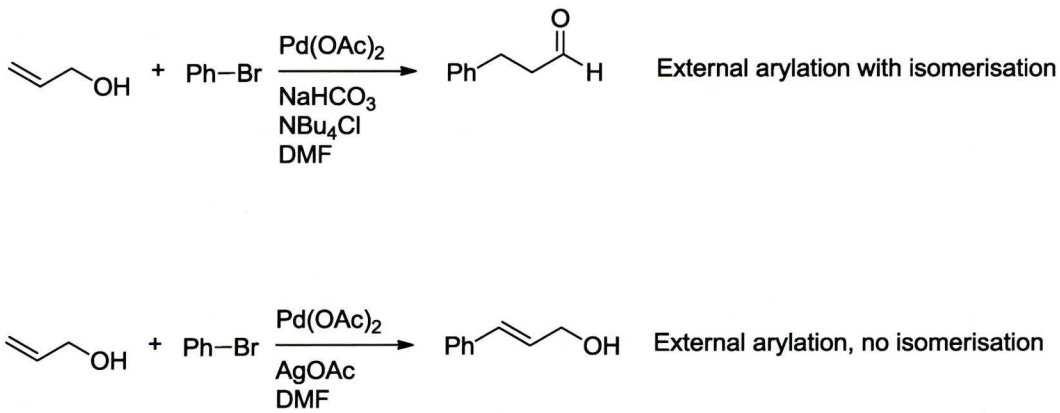
33 examples
Isolated yields 70-94%

n	Internal:external
1	>99:1
2	80:20
3	88:12
4	86:14
5	84:16
6	85:15

Scheme 4.07. Regioselective arylation of unsaturated alcohols in ionic liquid-DMSO

As well as controlling the regioselectivity of the arylation, it is also important to be able to control the chemoselectivity. Although the carbonyl products generated by the isomerisation pathway are useful, the initially produced substituted alcohols are also important compounds. To this end, a handful of reports have shown strategies for preventing the isomerisation.

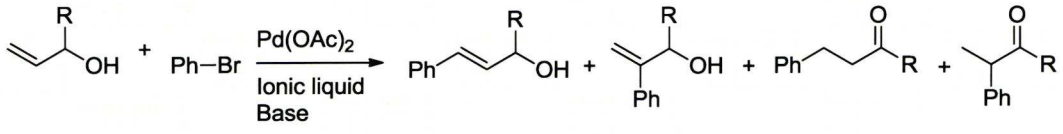
The phase transfer conditions developed by Jeffery (Chapter 1) were applied to the Heck reaction of unsaturated alcohols and allowed for mild reaction conditions.[46] The arylation of allyl alcohol was complete after 24 h at room temperature with 1 mol% $Pd(OAc)_2$, $NaHCO_3$ (2.5 eq) in DMF and 1 eq NBu_4 (Scheme 4.08). However, the products were still the carbonyl compounds resulting from the terminal arylation/isomerisation pathway. The same author reported that exchanging $NaHCO_3/NBu_4$ for AgOAc, although still leading to terminal arylation, completely inhibited the isomerisation pathway.[29] The terminally arylated (*E*)-alcohols were obtained with excellent, chemo-(alcohol vs. carbonyl), regio- (terminal vs. internal) and stereo-(*E/Z)* control.



Scheme 4.08. Jefferey's conditions for chemoselective unsaturated alcohol arylation

Spinelli and co-workers reported the arylation of unsaturated alcohols using a Pd-benzothiazole carbene complex in molten tetrabutylammonium bromide (TBAB) as solvent.[33] The reaction in this ionic liquid was initially reported to proceed with high external selectivity and yield the aryl ketones exclusively in good yield. They later discovered that, using $Pd(OAc)_2$ as catalyst, the nature of the ionic liquid and base could have a profound effect on the selectivity of the reaction. In the arylation

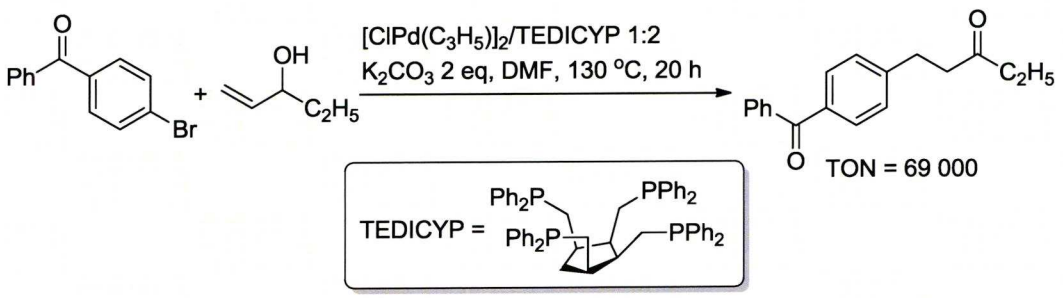
of a secondary allylic alcohol, switching from TBAB and $NaHCO_3$ to tetrabutylammonium acetate (TBAA) as base and solvent the selectivity changed to favour the substituted allylic alcohol. Isomerisation to the ketone was almost completely inhibited (Scheme 4.09).



Ionic liquid	Base	a	b	c	d
TBAB	$NaHCO_3$	0	0	97	3
TBAA	TBAA	90	6	4	0

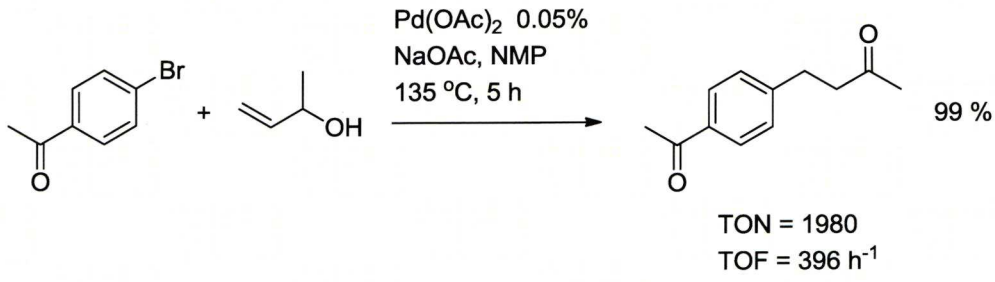
Scheme 4.09. Effect of ionic liquid and base on chemoselective arylation of allylic alcohols, R= C_5H_{11}

Other catalysts worthy of note for efficiency or favourable conditions are those reported by the groups of de Vries, Nejera and Santelli. Santelli reported the most efficient ligated palladium catalyst to date. The palladium tetraphoshine catalyst in scheme 4.10 applied so successfully to the arylation of unsaturated ketones and hydroxyl alkyl vinyl ethers was also found to be efficient for the regioselective terminal arylation of unsaturated alcohols.[35] S/C ratios of 100 000:1 were emplyed, yields were only moderate to good (best TON = 69 000); S/C = 10 000 allowed for consistently excellent yields (90-95%).



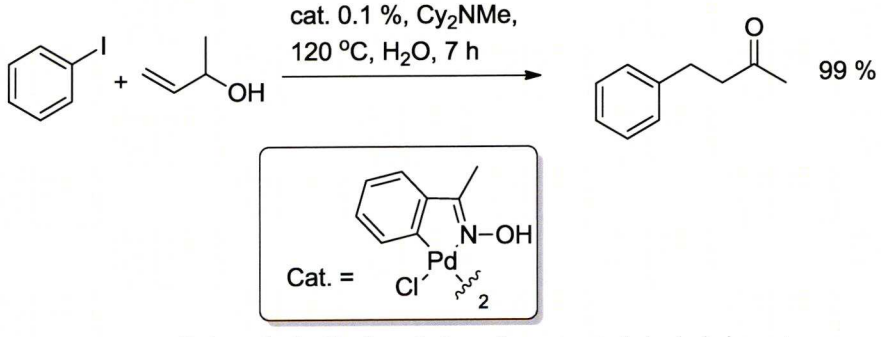
Scheme 4.10. Tedicyp as a ligand for the arylation of unsaturated alcohols

de Vries and co-workers' protocol for the arylation of 3-butene-2-ol provided the highest turnover numbers for these olefins and aryl bromides using a ligand free catalyst.[47] Scheme 4.11 shows how TON = 1980 and TOF <400 h^{-1} were achieved in the arylation of an unsaturated alcohol when $Pd(OAc)_2$ was employed as the precatalyst.



Scheme 4.11. Ligand free Heck arylation of unsaturated alcohols at low Pd-loading

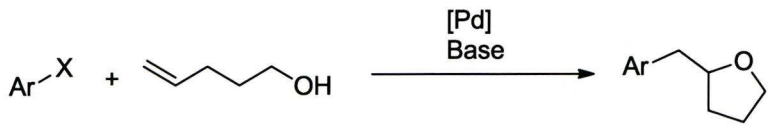
Najera's oxime-derived palladacycle was applied to unsaturated alcohol arylation in aqueous environments.[36] Scheme 4.12 shows how the complex was used as a precatalyst for the aryation of 3-butene-1-ol with iodobenzene in neat water. After 7 h at reflux with 0.1% Pd loading a 99% yield was achieved. The product distribution was around 85% in favour of 4-butanone with smaller amounts of the other ketone and alcohols. The catalyst could be recycled for 3 times before the yield dropped from~85 to 44%. The product selectivity in the recycles varied significantly.



Scheme 4.12. Najera's palladacycle for Heck arylation of unsaturated alcohols in water

THF's via carboetherification

Perhaps most relavent to this thesis is the work of Wolfe and co-workers.[48-57] They developed a reaction that, starting from aryl halides and unsaturated alcohols generates substituted THF's under palladium catalysis.[48,49,55,57] The compounds they obtained are isomers of our intended targets and are possible side products in our reaction. A general scheme for the reaction is shown in Scheme 4.13.



4.13. General scheme for Wolfe's palladium-catalysed carboetherification reaction

The key to obtaining a good yield was found to be in the choice of ligand and base. Hence, when $Pd_2(dba)_3$/P(2-tol)$_3$ with Ag_2CO_3 was employed as catalyst, the reaction yield was only 3-4% for the desired products. However, switching to $Pd_2(dba)_3$/DPE-Phos with NaO^{t}Bu dramatically increased the yield of the substituted THF to 76%.[57] Interestingly, only trace quantities of the Heck-type products were formed.

The reaction shows an excellent scope and tolerates a wide variety of alcohols and aryl bromides. In cases where there is more than one product possible, the diastereoselectivity is generally high. In an analogous carboamination for the synthesis of nitrogen heterocylcles, a change in the ligand to dppe and sovent to toluene was necessary to avoid the competing N-arylation reaction. The compounds accessible by these methodologies now include, THF's,[48,49,53,57] pyrrolidines,[58] imidazolidin-2-ones,[59] isoxazolidines,[50,60] piperazines[61,62] and morpholines.[63] Selected examples are shown in Figure 4.14.

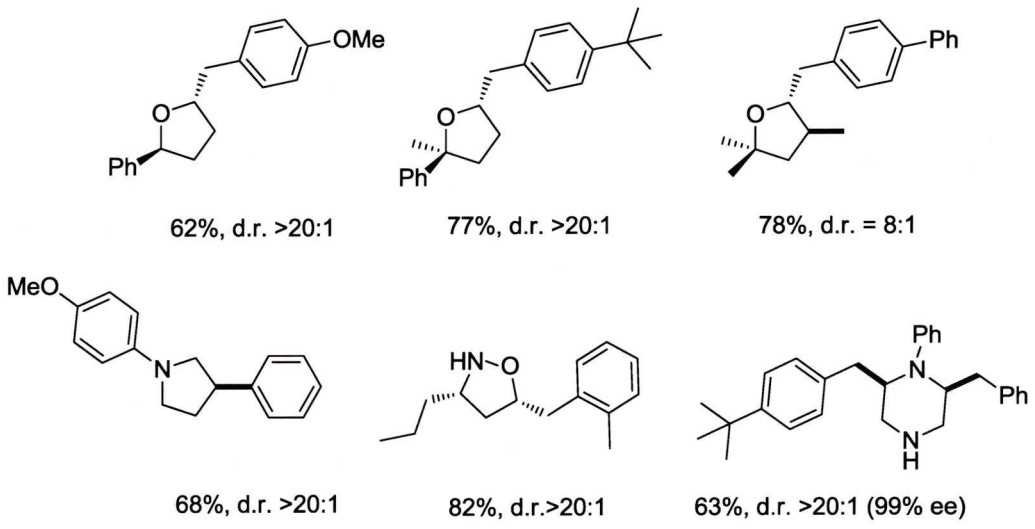
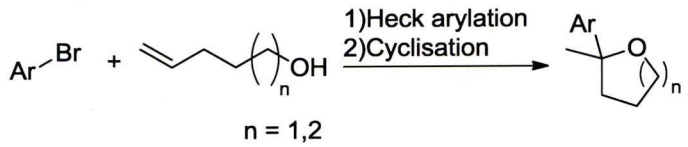


Figure 4.14. Examples of Wolfe's carboetherification/carboamination products

4.2 Results and Discussion

Given the importance of the compounds discussed in the introduction to this chapter, we thought it worthwhile to pursue a reaction whereby they can be made in a simple procedure from readily available starting materials. We envisaged a one-pot procedure comprising of a regioselective internal Heck arylation of unsaturated alcohols followed by an acid-catalysed intramolecular hydroalkoxylation (Scheme 4.14). The desired products, depending on the alcohol chosen, were 2,2-disubstituted THF's or THP's.

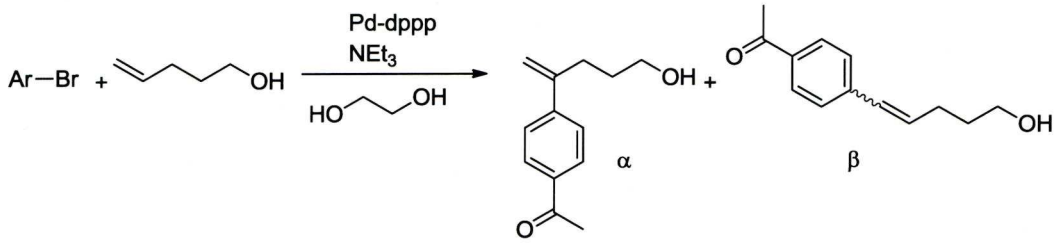


Scheme 4.14 Proposed one-pot procedure for THF and THP synthesis

Our first task was to find suitable conditions for the arylation of the unsaturated alcohols. Due to the success enjoyed by this group when alcohol solvents were employed for regioselective arylations of electron-rich olefins, we initially focused our efforts on developing the reaction for unsaturated alcohols in ethylene glycol.[64] The coupling of 4-bromoacetophenone with pent-4-ene-1-ol was chosen as a model reaction. The results obtained at various temperatures and catalyst concentrations are shown in table 4.01. Although complete conversion was possible in just 1.5 h at 145 °C with a 1% Pd loading, the isolated yield was only 60% of the isomeric mixture of alcohols. Reducing the temperature to 100 °C gave only marginal improvement to 65%. Lowering the Pd-loading to 0.1% led to a sluggish reaction that was not complete after 36 h (entry 3). The key to achieving a high yield for this reaction turned out to be a further reduction in temperature to 80 °C although a slight increase in catalyst loading was required for complete conversion in 12 h. An 86% yield and α:β ratio of 85:15 resulted.

The next step was to attempt a one-pot Heck/cyclisation procedure. After the Heck reaction was complete the reaction mixture was cooled to room temperarure and 3 eq of a bronsted acid were added. Two equivalents were required to neutralise the remaing NEt_3 from the Heck reaction, one equivalent to promote cyclisation. Much to our disappointment we did not obtain the desired tetrahydrofuran under any of the conditions tried (acids, co-solvents, temperature). Although complete consumption of the substituted alcohol was observed indicating a reaction had taken place, we have not, as yet, identified the products. We suspect the alcohol solvent is responsible for the failure of this approach to produce the desired products.

Table 4.01. Optimisation of unsaturated alcohol arylation in ethylene glycol[a]



Entry	Pd:dppp (mol%)	Base	T (°C)	Time (h)	Conv. (%)	α:β	Yield[b]
1	1:2	NEt_3	145	1.5	100	85:15	60
2	1:2	3eq NEt_3	100	5	100	84:16	65
3	0.1:0.2	3eq NEt_3	100	36	80	85:15	-
4	1:3	3eq NEt_3	100	5	100	86:14	-
5	1:2	3eq NEt_3	80	30	100	85:15	85
6	1.5:3	3 eq NEt_3	80	12	100	85:15	86
7	1.5:3	1.2eq NEt_3	80	12	75	85:15	-

[a] Reaction conditions: 4-bromoacetophenone (1 mmol) , 4-pentene-1ol (1.2mmol) , $Pd(OAc)_2$, dppp, NEt_3, 1 mL ethylene glycol
[b] Isolated yields (isomeric mixture of alcohols).

We were then faced with the finding alternative conditions for the Heck rection. Previous work in this group had shown that the Heck arylation of unsaturated alcohols could be performed in a 1:1 mixture of DMSO and an imidazolium based ionic liquid.[44] We wondered whether it might be possible to replace the ionic liquid with the H-bond donating salts that had been successful for other reactions of electron-rich olefins, a cheaper altrernative.[65] A screening of conditions was undertaken and the results are shown in table 4.02.

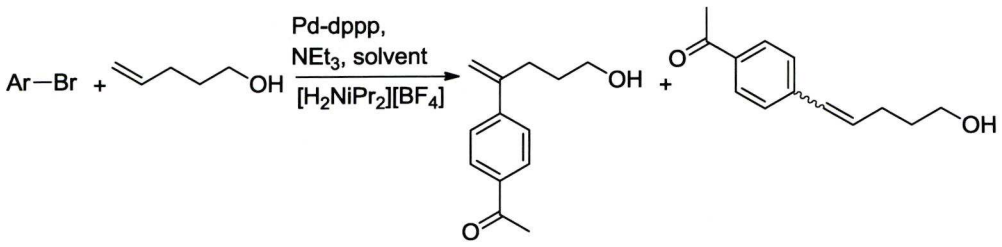
Entry 1 shows that the addition of $[H_2N^iPr_2][BF_4]$ (1.5 eq.) to DMSO allowed us to obtain the required substituted alcohol in 75% yield with an α:β ratio of 80:20.

In the absence of the ammonium salt the selectivity and yield were both significantly diminished (entry 2). DMF also gave satisfactory results when used in conjunction with the H-bond donor (entry 3). Toluene, although affording acceptable regioselectivity, gave only a moderate yield of the desired product (entry 4). Acetonitrile proved to be an excellent solvent for our reaction, giving a promising 83% yield and 75:25 α:β ratio (entry 5). Although no reaction was observed in dioxane in the absence of the ammonium salt, the regioselectivity obtained was the highest of all when 1.5eq $[H_2N^iPr_2][BF_4]$ was added (entries 6 & 7). A further increase to 3 equivalents of the additive had negligible effect on the regioselectivity or isolated yield (entry 8). It should also be noted that double bond migration occurred in all reactions to give the tri-substituted alkene shown in Table 4.02. This was not a concern, however, as the product of cyclisation would be the same as that for the terminal olefin initially produced by the Heck reaction.

It is important at this point to address the selectivity of the reaction towards the Heck products. We realise that the conditions we used for the Heck reaction, particularly entries 7 and 8, are very similar to those employed by Wolfe for the carboetherification reactions (etheral solvent, Pd, bisphosphine, base). However, Wolfe proposes a mechanism that includes insertion of an alkene into a Pd-oxygen bond.[48] This is an unusual step with little in the way of literature precedent for unactivated alkenes.[66-68] It is suggested that the strong base necessary for the successful reaction is required to increase the nucleophilicity of the oxygen atom and facilitate the insertion. We presume that under our conditions (NEt_3) the nucleophilicity of the oxygen atom is not sufficient for this process to occur and the

more usual insertion of olefin into the Pd-Ar bond is faster. Hence, the Heck reaction is the dominant pathway.

Table 4.02. Development of alternative arylation conditions[a]

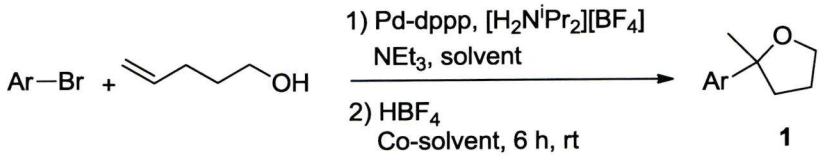


Entry	Solvent	Additive	α:β	Isomerisation (% of α)	Yield[b]
1	DMSO	1.5	80:20	17	75
2	DMSO	None	55:45	72	60
3	DMF	1.5	75:25	87	72
4	Toluene	1.5	82:18	27	50
5	MeCN	1.5	74:26	69	83
6	Dioxane	None	-	-	-
7	Dioxane	1.5	85:15	25	75
8	Dioxane	3	84:15	28	73

[a] Reaction conditions: 4-bromoacetophenone (1 mmol) , 4-pentene-1ol (1.2mmol) , $Pd(OAc)_2$ (0.03 mmol), dppp (0.06 mmol), NEt_3 (3 mmol), 1 mL solvent, 110 °C, 24 h
[b] Isolated yields (isomeric mixture of alcohols)

With a promising variety of conditions in hand, we turned our attention to developing a one pot procedure. After completion of the Heck reaction, the flask was cooled to room temperature and 6 mL of a co-solvent and 3 equivalents of an acid were added. 2 equivalents of acid were required to neutralise the excess NEt_3 left after the Heck reaction and one equivalent to afford cyclisation of the unsaturated alcohol. The results using various solvents/co-solvents are shown in Table 4.03.

Table 4.03. Development of one-pot Heck/Cyclisation procedure[a]



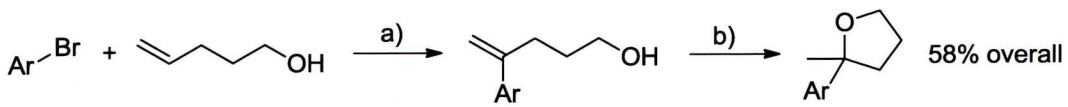
Entry	Solvent	'Co-solvent'	Acid	Yield[b]
1	Dioxane	Toluene	HBF_4	50
2	Dioxane	Toluene	Conc. H_2SO_4	33
3	Dioxane	Toluene	Conc. HNO_3	28
4	DMSO	DMSO	HBF_4	0
5	DMSO	DMSO	TfOH	0
6	MeCN	MeCN	HBF_4	22
7	MeCN	MeCN	TfOH	15
8	Dioxane	None	HBF_4	28
9	Dioxane	Dioxane	HBF_4	40
10	Dioxane	Hexane	HBF_4	62
11	Dioxane	DCM	HBF_4	52

[a] Reaction conditions: 4-bromoacetophenone (1 mmol) , 4-pentene-1ol (1.2mmol) , $Pd(OAc)_2$ (0.03 mmol), dppp (0.06 mmol), NEt_3 (3 mmol), 1 mL solvent, 110 °C, 24 h then 3 eq. Acid, 6 mL co-solvent, rt, 12 h.
[b] Isolated Yields

It was decided to first use toluene as the co-solvent as it has been used in previous reports on cyclisations of this type. Using HBF_4 with this solvent system led to a 50% yield of **1** over the two steps but changing to the weaker H_2SO_4 or HNO_3 reduced this value to 33 and 28% respectiviely (entries 1-3). Although complete consumption of the alcohol was observed in DMSO, no **1** was obtained, regardless of the acid chosen (entries 4 & 5). MeCN had proved to be an excellent solvent for the initial arylation but upon addition of TfOH or HBF_4 only low yields of **1** were obtained (entries 6 & 7). Entries 8 and 9 show that addition of the co-solvent has

significant benefit for the yield of the reaction. Hence, when dioxane was used without a co-solvent the yield dropped to 28% compared with 40% for the dioaxane/dioxane system. We were delighted to find that the use of hexane as the co-solvent with dioxane allowed us to obtain the desired 2,2-disubstituted THF **1** in a 62% isolated yield (entry 10). Although providing a respectable 52%, DCM was inferior to hexane as a co-solvent so it was decided to continue our investigation with the dioxane/hexane system as optimal conditions.

To see how our one-pot procedure compares to a two-step synthesis, with isolation of the intermediate alcohol, we first carried out the Heck reaction under our best conditions found in table 4.01. After isolation we subjected the substituted alcohol to cyclisation with HBF_4 in dioxane. The overall yield was 58% based on the starting bromide (Scheme 4.15). This compares favourably with our method as the yields are similar (62%) and one-pot processes are always favoured over multi-step syntheses.

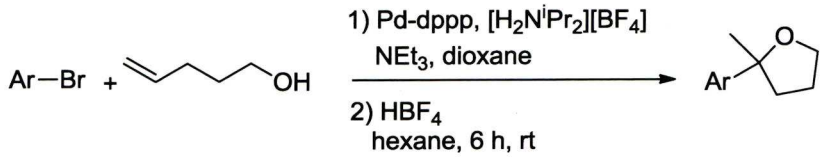


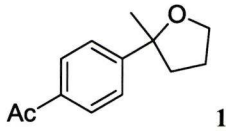
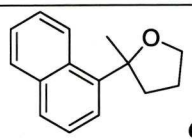
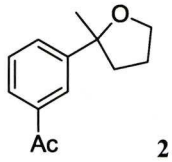
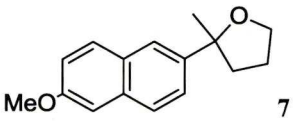
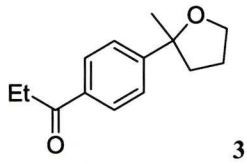
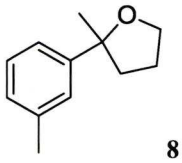
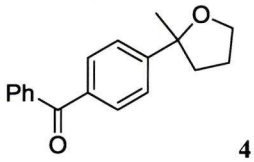
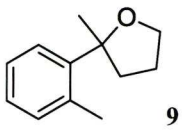
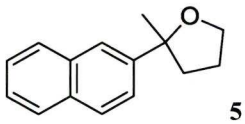
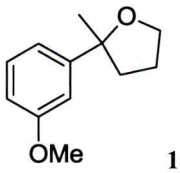
a) Conditions as in table 4.01, entry 5, b) 0.5 eq HBF_4, dioxane 4 mL, rt, 8 h

Scheme 4.15. Two step synthesis of substituted THF

We then focussed our efforts on expanding the scope of the reaction with respect to the aryl bromide. The results are shown in Table 4.04. A range of aryl bromides are tolerated and converted smoothly into the corresponding alcohol and eventually the 2,2-disubtituted THF's in moderate to good yields. Electron deficient (entries 1-6), electron-rich (entries 7-10) and sterically demanding (entries 6 and 9) substrates can all be tolerated by the convenient one-pot procedure.

Table 4.04. THFs by a one-pot Heck arylation/cyclisation procedure[a]

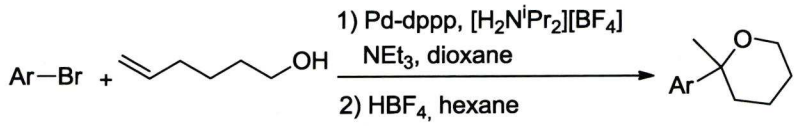


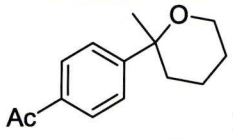
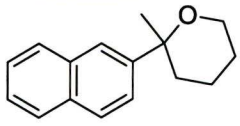
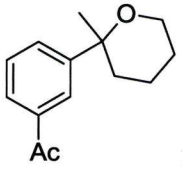
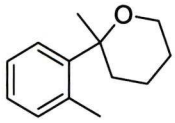
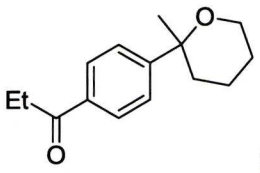
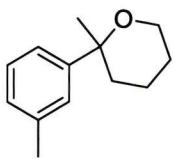
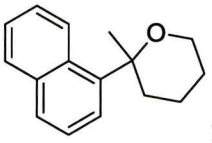
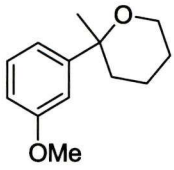
Entry	Product	Yield[b]	Entry	Product	Yield[b]
1	 **1**	62	6	 **6**	51
2	 **2**	55	7	 **7**	50
3	 **3**	54	8	 **8**	62
4	 **4**	55	9	 **9**	58
5	 **5**	54	10	 **10**	65

[a] Reaction conditions: ArBr (1 mmol) , 4-pentene-1ol (1.2 mmol) , $Pd(OAc)_2$ (0.03 mmol), dppp (0.06 mmol), NEt_3 (3 mmol), 1 mL solvent, 110 °C, 24 h then HBF_4 (2.3-3eq),hexane 6 mL, rt, 3-8 h.
[b] Isolated yields

In order to further expand the scope of the reaction we investigated the possibility of changing the starting unsaturated alcohol with a vue to producing different ring sizes. Hence, 5-hexene-1-ol was reacted under conditions similar to those in Table 4.03 with a range of aryl bromides to yield a variety of 2,2-substituted tetrahydropyrans in the moderate yields reported in Table 4.05. The lower yields were attrbuted to an inherently lower regioselectivity in the Heck reaction for this alcohol (75:25 *vs* 85:25).

Table 4.05. THP's by a one-pot Heck arylation/cyclisation procedure



Entry	Product	Yield[b]	Entry	Product	Yield[b]
1	 **11**	41	5	 **15**	45
2	 **12**	43	6	 **16**	42
3	 **13**	40	7	 **17**	48
4	 **14**	40	8	 **18**	53

[a] Reaction conditions: ArBr (1 mmol) , 5-hexene-1-ol (1.2 mmol) , $Pd(OAc)_2$ (0.03 mmol), dppp (0.06 mmol), NEt_3 (3 mmol), 1 mL solvent, 110 °C, 24 h then HBF_4 (2.3-3 eq),Hexane 4 mL, rt, 3-8 h.
[b] Isolated yields

We next turned our attention to aryl bromides that contained more than one bromine atoms. Our intentions were twofold-

1. To see if it is possible to affect a monosubstitution and hence obtain polycyclic systems that could then be reacted in further coupling reactions.

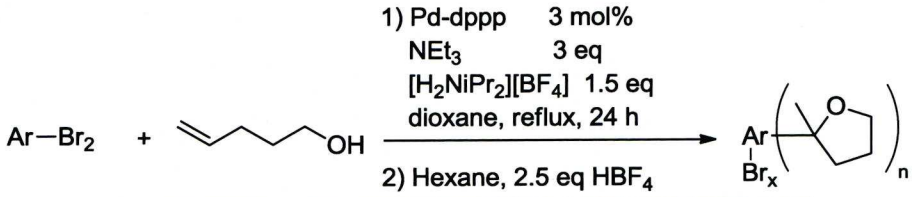
2. Perform multiple substitution/cyclisation reactions to produce tetracyclic products.

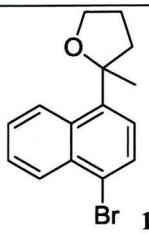
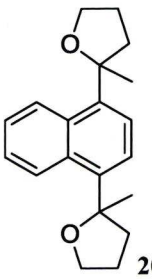
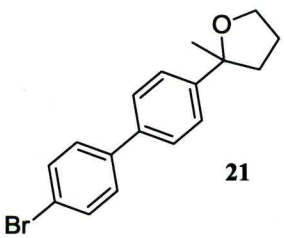
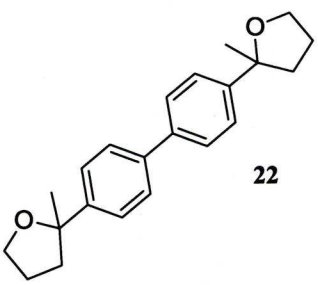
We thought this might be possible by controlling the stoichiometry of the reaction (i.e. the amount of alcohol). Hence, when 1.05 eq of pent-4-ene-1-ol was added to the reaction of 1,4-dibromonapthalene and the procedure described in Table 4.04 was repeated, a 35% yield of the desired monosubstituted product shown in Table 4.06, entry 1 was obtained. Unreacted starting material and disubstituted product were also obtained in 10 and 9% yields, respectiviely. Repeating the procedure with 4,4'-dibromobiphenyl (entry 3) led to a 28% yield with similar amounts of the starting material and disubtituted product obtained as in entry 1. The same two substrates were then reacted with 2.5 eq of pent-4-ene-1-ol and subjected to the same cyclisation conditions as before (2.5 eq HBF_4, hexane). The tetracyclic products shown in entries 2 and 4 demonstrate how the chemistry developed here can be used to construct polyheterocyclic compounds, albeit in modest yields.

The fact that our products contain a quaternary stereogenic centre did not go unnoticed. As this centre is generated during the acid-catalysed cyclisation, we thought a chiral brønstead acid might allow us to obtain chiral substituted THFs. However, a chiral binol phosphoric acid did not provide any conversion at any of the loadings (1-10 mol%) or temperatures (rt-80 °C) tried. The chiral (+)-camphorsulfonic acid (20 mol%) gave only 25% of conversion to the desired product in 48 h at 60 °C which, disappointingly, was a racemic mixture.

We also contemplated the use of higher unsaturated alcohols as a way to access larger oxygen heterocycles. All the alcohols tried reacted smoothly with 4-bromoacetophenone to yield the substituted alcohol. Unfortunately, none of the Heck products were cyclised under the conditions employed for the THFs and THPs above.

Table 4.06 One-pot Heck/Cyclisation procedure for aryl dibromides



Entry	Alcohol (eq)	Product	Yield[c]
1[a]	1.05	 **19**	35
2[b]	1.05	 **20**	27
3[a]	2.5	 **21**	28
4[b]	2.5	 **22**	24

[a] 1 mmol aryl bromide, 1.05 mmol 4-pentene-1-ol
[b] 1 mmol aryl bromide, 2.25 mmol 4-pentene-1-ol
[c] Isolated yields

4.3. Conclusions and Future Work

A one-pot procedure for the synthesis of substituted THFs and THPs from aryl bromides and unsaturated alcohols has been developed. The regioselective internal arylation of unsaturated alcohols followed by an acid promoted cyclisation allows for a variety of 2,2-disubstituted oxygen heterocyles to be produced in moderate to good yields. Because other methodologies for the Heck arylation were unsuitable, new conditions were developed for this work. The use of an H-bond donating salt $[H_2NiPr_2][BF_4]$ in molecular solvents allowed for regioselectivities similar to those achieved in previous reports and successful cyclisation. To the best of our knowledge, this is the first example of a one-pot two-step procedure involving the internal arylation of an unsaturated alcohol, affording THFs and THPs.

The conditions for the cyclisation reported in this work are highly acidic (1 eq HBF_4) and may not be attractive for complex synthetic applications. Taking advantage of other methods of cyclisation such as iodocyclisation or the metal triflate mediated protocol would provide a more versatile procedure. Halocyclisation in particular would be an interesting development as this installs a synthetic handle for further elaboration. By replacing the unsaturated alcohols with unsaturated acids the scope could be opened up to include lactone-type products. A recent report indicates that more water-soluble electron-rich olefins allow regioselective arylation to be performed in aqueous environments. As this is also true for some of the alternative cyclisation procedures discussed, an aqueous one-pot procedure for the arylation/cyclisation might be possible. The products presented here were all racemic mixtures, development of an asymmetric cyclisation to couple with the arylation would add significant value to the present work.

4.4 Experimental

General procedure for the Heck arylation of unsaturated alcohols in ethylene glycol. An oven-dried, two-necked round-bottom flask containing a stir bar was charged with $Pd(OAc)_2$ (0.01 mmol, 2.2 mg), dppp (0.02 mmol, 6.4 mg), 4-bromoacetophenone (1 mmol, 199 mg), 4-pentene-1-ol (1.2 mmol, 103 mg, 0.12 mL) and 1 mL ethylene glycol. The flask was degassed and backfilled with nitrogen for three times and NEt_3 (3 mmol, 303 mg, 0.4 mL) was injected. The flask was heated to 80 °C for an appropriate time until tlc. analysis showed consumption of the aryl bromide was complete. The flask was cooled to room temperature and water (10 mL) was added. The mixture was extracted with Et_2O (3 x 15 mL) and the combined organic layers were concentrated *in vacuo*. The crude mixture was subjected to NMR analysis and then purified by flash chromatography on silica gel (hexanes:EtOAc, 9:1). The results are shown in Table 4.01 of the text.

Optimisation of Heck arylation of unsaturated alcohols in molecular solvents. An oven-dried, two-necked round-bottom flask containing a stir bar was charged with $Pd(OAc)_2$ (0.03 mmol, 6.7 mg), dppp (0.06 mmol, 24.6 mg), salt additive, 4-bromoacetophenone (1 mmol, 199 mg) and 4-pentene-1-ol (1.2 mmol, 103 mg, 0.12 mL) and 1 mL of solvent. The flask was degassed and backfilled with nitrogen for three times and NEt_3 (3 mmol, 303 mg, 0.4 mL) was injected. The flask was heated (block temperature 115 °C) and the mixture stirred vigorously for an appropriate time. The flask was cooled to room temperature and water (10 mL) was added. The mixture was extracted with Et_2O (3 x 15 mL) and the combined organic layers were concentrated *in vacuo*. The crude mixture was subjected to NMR analysis and then purified by flash chromatography on silica gel (hexanes:EtOAc, 9:1).

Optimisation of one-pot procedure for the synthesis of substituted THFs and THPs. An oven-dried, two-necked round-bottom flask containing a stir bar was charged with $Pd(OAc)_2$ (0.03 mmol, 6.7 mg), dppp (0.06 mmol, 24.6 mg), $[H_2N_iPr_2][BF_4]$ (1.5 mmol, 283 mg), 4-bromoacetophenone (1 mmol, 199 mg) and 4-pentene-1-ol (or 5-hexene-1-ol) (1.2 mmol, 103 mg, 0.12 mL) and 1 mL dioxane. The flask was degassed and backfilled with nitrogen for three times and NEt_3 (3 mmol, 303 mg, 0.4 mL) was injected. The flask was heated (block temperature 115 °C) and the biphasic mixture stirred vigorously until tlc. analysis revealed total consumption of the aryl bromide. The mixture was cooled to room temperature and, where appropriate, 6 mL of a co-solvent and 3 mmol of acid were injected sequentially. The biphasic mixture was stirred vigorously until tlc. analysis showed consumption of the substituted alcohol was complete (or for 24 h) and NEt_3 (2 mmol, 0.27 mL, 202 mg) and water (15 mL) were added and the mixture extracted with Et_2O (3 x 15 mL). The combined extracts were concentrated *in vacuo* and the crude residue purified by flash chromatography on silica gel (hexanes:EtOAc, 98:2).

General procedure for the one-pot synthesis of 2,2'-disubstituted THFs and THPs from aryl bromides and unsaturated alcohols. An oven-dried, two-necked round-bottom flask containing a stir bar was charged with $Pd(OAc)_2$ (0.03 mmol, 6.7 mg), dppp (0.06 mmol, 24.6 mg), $[H_2N_iPr_2][BF_4]$ (1.5 mmol, 283 mg), 4-bromoacetophenone (1 mmol, 199 mg) and 4-pentene-1-ol (or 5-hexene-1-ol) (1.2 mmol, 103 mg, 0.12 mL) and 1 mL dioxane. The flask was degassed and backfilled with nitrogen for three times and NEt_3 (3 mmol, 303 mg, 0.4 mL) was injected. The flask was heated (block temperature 115 °C) and the biphasic mixture stirred vigorously until tlc. analysis revealed total consumption of the aryl bromide. The

mixture was cooled to room temperature and hexane (6 mL) and HBF_4. (54% wt. in Et_2O) (3 mmol) were injected sequentially. The biphasic mixture was stirred vigorously until tlc. analysis showed consumption of the substituted alcohol was complete. NEt_3 (2 mmol, 0.27 mL, 202 mg) and water (15 mL) was added and the mixture extracted with Et_2O (3 x 15 mL). The combined extracts were concentrated *in vacuo* and the crude residue purified by flash chromatography on silica gel (hexanes:EtOAc, 98:2).

4.5 Compounds characterised

1-(4-(2-methyltetrahydrofuran-2-yl)phenyl)ethanone 1

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.4 Hz, 2 H), 7.49 (d, *J* = 8.4 Hz, 2 H), 4.15-3.99 (m, 1 H), 3.98-3.88 (m, 1 H), 2.60 (s, 3 H), 2.29-2.13 (m, 1 H), 2.13-1.94 (m, 2 H), 1.89-1.75 (m, 1 H), 1.53 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.5, 152.5, 129.4, 126.1, 113.4, 82.5, 69.1, 39.5, 30.0, 28.2, 26.7

CI-HRMS Calcd for $C_{13}H_{17}O_2$ $(M + H)^+$: 205.1223. Found: 205.1223

Anal Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.40; H, 7.89

1-(3-(2-methyltetrahydrofuran-2-yl)phenyl)ethanone 2

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (t, *J* = 1.6 Hz, 1 H), 7.82 (dt, *J* = 7.6, 1.2 Hz, 1 H), 7.65-7.61 (m, 1 H), 7.42 (t, *J* = 9.2 Hz, 1 H), 4.08-4.00 (m, 1 H), 3.96-3.89 (m, 1 H), 2.62 (s, 3 H), 2.27-2.16 (m, 1 H), 2.11-1.95 (m, 2 H), 1.89-1.75 (m, 1 H), 1.54 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.2, 149.3, 137.2, 130.0, 128.8, 127.0, 124.9, 84.5, 68.1, 39.9, 30.0, 27.2, 26.2

CI-HRMS Calcd for $C_{13}H_{20}O_2N$ $(M + NH_4)^+$: 222.1489. Found: 222.1491

Anal Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.50; H, 7.93

1-(4-(2-methyltetrahydrofuran-2-yl)phenyl)propan-1-one 3

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.4 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H), 4.11-4.00 (m, 1 H), 3.97-3.88 (m, 1 H), 2.99 (q, *J* = 7.2 Hz, 2 H), 2.25-2.14 (m, 1 H), 2.12-1.94 (m, 2 H), 1.86-1.75 (m, 1 H), 1.54 (s, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 200.7, 144.6, 135.6, 128.4, 124.8, 84.7, 68.1, 36.4, 29.8, 26.2, 8.6

CI-HRMS Calcd for $C_{14}H_{19}O_2$ $(M + H)^+$: 219.1385. Found: 219.1387

Anal Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.15; H, 8.33

(4-(2-methyltetrahydrofuran-2-yl)phenyl)(phenyl)methanone 4

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85-7.75 (m, 4 H), 7.62-7.55 (m, 1 H), 7.54-7.45 (m, 4 H), 4.10-4.00 (m, 1 H), 3.99-3.90 (m, 1 H), 2.28-2.18 (m, 1 H), 2.14-1.95 (m, 2 H), 1.89-1.75 (m, 1 H) 1.56 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.9, 153.5, 138.2, 136.1, 132.7, 130.8, 130.6, 128.7, 125.4, 84.7, 68.2, 39.9, 29.6, 26.1

CI-HRMS Calcd for $C_{18}H_{18}O_2Na$ $(M + Na)^+$: 289.1204. Found: 289.1197

Anal Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.39; H, 6.85

2-methyl-2-(naphthalen-2-yl)tetrahydrofuran 5

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96-7.78 (m, 4 H), 7.56-7.40 (m, 3 H), 4.12-4.03 (m, 1 H), 4.03-3.95 (m, 1 H), 2.35-2.27 (m, 1 H), 2.15-1.95 (m, 2 H), 1.90-1.75 (m, 1 H), 1.60 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.9, 133.6, 132.6, 128.5, 128.3, 127.9, 126.4, 125.9, 124.2, 123.2, 84.8, 68.1, 39.8, 30.0, 26.2

CI-HRMS Calcd for $C_{15}H_{17}O$ $(M + H)^+$: 213.1274. Found: 213.1270

Anal Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.95; H, 7.62

2-methyl-2-(naphthalen-1-yl)tetrahydrofuran 6

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31- 8.13 (m, 1 H), 7.99-7.67 (m, 3 H), 7.64-7.34 (m, 3 H), 4.17 (td, J = 8.0, 4.8 Hz, 1 H), 3.97-3.78 (m, 1 H), 2.64-2.56 (m, 1 H), 2.53-2.29 (m, 1 H), 2.22-1.96 (m, 1 H), 1.94-1.80 (m, 1 H), 1.82 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.1, 135.2, 130.4, 129.7, 128.8, 128.3, 126.4, 125.8, 125.6, 122.9, 85.0, 67.1, 39.8, 30.1, 26.9

CI-HRMS Calcd for $C_{15}H_{17}O$ $(M + H)^+$: 213.1274. Found: 213.1270

Anal Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 85.10; H, 7.65

2-(6-methoxynaphthalen-2-yl)-2-methyltetrahydrofuran 7

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (s, 1 H), 7.71 (t, *J* = 9.2 Hz, 2 H), 7.45 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.17-7.10 (m, 2 H), 4.11-4.02 (m, 1 H), 4.02-3.94 (m, 1 H), 3.91 (s, 3 H), 2.36-2.25 (m, 1 H), 2.15-1.95 (m, 2 H), 1.90-1.76 (m, 1 H), 1.59 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.9, 143.6, 133.7, 129.9, 129.1, 127.1, 124.7, 123.1, 119.1, 105.9, 84.8, 68.0, 55.7, 39.8, 30.1, 26.2

ES-HRMS Calcd for $C_{16}H_{18}O_2Na$ $(M + Na)^+$: 265.1204. Found: 265.1194

Anal Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.60. Found: C, 79.25; H, 7.58

2-methyl-2-(m-tolyl)tetrahydrofuran 8

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31-7.15 (m, 3 H), 7.06-7.00 (m, 1 H), 4.08-3.97 (m, 1 H), 3.95-3.86 (m, 1 H), 2.35 (s, 3 H), 2.27-2.14 (m, 1 H), 2.10-1.90 (m, 2 H), 1.85-1.74 (m, 1 H), 1.51 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.6, 138.1, 128.4, 127.5, 125.8, 122.2, 84.7, 67.9, 39.9, 30.2, 26.2, 22.0

CI-HRMS Calcd for $C_{12}H_{20}ON$ $(M + NH_4)^+$: 194.1539. Found: 194.1537

Anal Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.80; H, 9.16

2-methyl-2-(o-tolyl)tetrahydrofuran 9

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (m, 1 H), 7.25-7.09 (m, 3 H), 4.11-3.97 (m, 1 H), 3.90-3.74 (m, 1H), 3.44 (s, 3 H), 2.42-2.11 (m, 2 H), 2.12-1.92 (m, 1 H), 1.91-1.79 (m, 1 H), 1.54 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 146.4, 134.3, 132.4, 130.5, 127.0, 126.1, 125.5, 84.9, 67.2, 39.0, 28.6, 26.8, 22.0

CI-HRMS Calcd for $C_{12}H_{20}ON$ $(M + NH_4)^+$: 194.1539. Found: 194.1539

Anal Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.80; H, 9.16

2-(3-methoxyphenyl)-2-methyltetrahydrofuran 10

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (t, *J* = 8.0 Hz, 1 H), 6.99 (t, *J* = 2.0 Hz, 1 H), 6.98 (m, 1 H), 6.75 (dd, *J* = 8.0, 2.4 Hz, 1 H), 4.07-3.96 (m, 1 H), 3.95-3.87 (m, 1 H), 3.81 (s, 3 H), 2.26-2.15 (m, 1 H), 2.08-1.90 (m, 2 H), 1.87-1.75 (m, 1 H), 1.52 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.9, 150.5, 129.6, 117.6, 111.9, 111.0, 84.7, 68.0, 55.6, 39.9, 30.1, 26.2

CI-HRMS Calcd for $C_{12}H_{17}O_2$ $(M + H)^+$: 193.1223. Found: 193.1225.

Anal Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.81; H, 8.35

1-(4-(2-methyltetrahydro-2H-pyran-2-yl)phenyl)ethanone 11

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.4 Hz, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 3.83-3.73 (m, 1 H), 3.56-3.42 (m, 1 H), 2.61 (s, 3 H), 2.37-2.25 (m, 1 H), 1.86-1.55 (m, 3 H), 1.53-1.40 (m, 3 H), 1.39 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.3, 151.7, 135.9, 129.1, 126.6, 76.4, 63.4, 35.1, 27.0, 26.2, 20.5

CI-HRMS Calcd for $C_{14}H_{19}O_2$ $(M + H)^+$: 233.1541. Found: 233.1543

Anal Calcd for $C_{14}H_{18}O_2$: C, 77.55; H, 8.68. Found: C, 77.47; H, 8.64

1-(3-(2-methyltetrahydro-2H-pyran-2-yl)phenyl)ethanone 12

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (s, 1 H), 7.84 (d, *J* = 7.7, 1 H), 7.65 (d, *J* = 7.8, 1 H), 7.40 (t, *J* = 4.2 Hz, 1 H), 3.85-3.75 (m, 1 H), 3.54-3.42 (m, 1 H), 2.63 (s, 3 H), 2.40-2.27 (m, 1 H), 1.86-1.76 (m, 1 H), 1.74-1.58 (m, 2 H), 1.54-1.42 (m, 2 H), 1.40 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.8, 146.8, 137.8, 131.3, 129.2, 127.1, 126.1, 76.2, 63.3, 35.0, 32.5, 27.2, 26.3, 20.4

CI-HRMS Calcd for $C_{14}H_{19}O_2$ $(M + H)^+$: 233.1541. Found: 233.1541

Anal Calcd for $C_{14}H_{18}O_2$: C, 77.55; H, 8.68. Found: C, 77.72; H, 8.71

1-(4-(2-methyltetrahydro-2H-pyran-2-yl)phenyl)propan-1-one 13

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.8 Hz, 2 H), 7.43 (d, *J* = 8.8 Hz, 2 H), 3.74-3.65 (m, 2 H), 3.45-3.34 (m, 1 H), 2.98 (q, *J* = 7.4 Hz, 2 H), 1.77-1.50 (m, 2 H), 1.46-1.31 (m, 2 H), 1.30 (s, 3 H), 1.15 (t, *J* = 7.4 Hz, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 200.9, 171.5, 151.4, 135.7, 128.7, 126.5, 76.4, 63.3, 35.0, 32.4, 32.2, 26.2, 8.7

CI-HRMS Calcd for $C_{15}H_{21}O_2$ $(M + H)^+$: 233.1541. Found: 233.1543

Anal Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.45; H, 8.64

2-methyl-2-(naphthalen-1-yl)tetrahydro-2H-pyran 14

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.11-9.01 (m, 1 H), 7.90-7.80 (m, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 7.57-7.37 (m, 4 H), 3.75-3.66 (m, 1 H), 3.19 (td, *J* = 9.2, 2.4 Hz, 1 H), 2.70-2.55 (m, 1 H), 1.95-1.80 (m, 2 H), 1.78-1.67 (m, 2 H), 1.67 (s, 3 H), 1.45-1.35 (m, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.7, 135.4, 132.5, 129.4, 128.8, 127.5, 126.2, 125.9, 125.7, 125.2, 79.0, 63.5, 36.7, 31.7, 26.0, 20.3

CI-HRMS Calcd for $C_{16}H_{22}ON$ $(M + NH_4)^+$: 244.1701. Found: 244.1703

Anal Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 85.12; H, 8.08

2-methyl-2-(naphthalen-2-yl)tetrahydro-2H-pyran 15

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89-7.80 (m, 4 H), 7.60 (dd, *J* = 8.8, 1.6 Hz, 1 H), 7.53-7.42 (m, 2 H), 3.84-3.74 (m, 1 H), 3.51 (td, *J* = 11.2, 2.8 Hz, 1 H), 2.53-2.41 (m, 1 H), 1.92-1.79 (m, 1 H), 1.78-1.54 (m, 3 H), 1.46 (s, 3 H), 1.45-1.37 (m, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.2, 133.9, 132.7, 128.7, 128.4, 127.9, 126.3, 126.1, 125.1, 125.0, 76.5, 63.4, 35.0, 33.1, 26.4, 20.6

CI-HRMS Calcd for $C_{16}H_{22}NO(M + NH_4)^+$: 244.1701. Found: 244.1701

Anal Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.99; H, 8.03

2-methyl-2-(o-tolyl)tetrahydro-2H-pyran 16

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28-7.22 (m, 1 H), 7.21-7.10 (m, 1 H), 3.80-3.67 (m, 1 H), 3.35-3.22 (m, 1 H), 2.51 (s, 3 H), 2.50-2.42 (m, 1 H), 1.80-1.62 (m, 4 H), 1.44 (s, 3 H), 1.43-1.36 (m, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.8, 137.8, 133.5, 128.1, 127.2, 126.1, 78.3, 63.1, 36.3, 30.6, 26.3, 22.4, 20.5

CI-HRMS Calcd for $C_{13}H_{22}NO$ $(M + NH_4)^+$: 208.1701. Found: 208.1702.

Anal Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.28; H, 9.57

2-methyl-2-(m-tolyl)tetrahydro-2H-pyran 17

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33-7.17 (m, 3 H), 7.10-7.03 (m, 1 H), 3.80-3.69 (m, 1 H), 3.49 (td, *J* = 10.8, 2.8 Hz, 1 H), 2.36 (s, 3 H), 2.34-2.25 (m, 1 H), 1.85-1.56 (m, 3 H), 1.55-1.40 (m, 2 H), 1.37 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.3, 147.6, 129.8, 118.7, 112.5, 111.9, 76.4, 63.3, 55.6, 35.0, 33.1, 26.3, 20.5

CI-HRMS Calcd for $C_{13}H_{22}NO$ $(M + NH_4)^+$: 208.1701. Found: 208.1700

Anal Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.15; H, 9.54

2-(3-methoxyphenyl)-2-methyltetrahydro-2H-pyran 18

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (t, *J* = 8.8 Hz, 1 H), 7.08-6.96 (m, 2 H), 7.78 (dd, *J* = 8.0, 2.8 Hz, 1 H), 3.81 (s, 3 H), 3.77-3.69 (m, 1 H), 3.50 (td, *J* = 11.2, 2.8 Hz, 1 H), (dt, *J* = 13.6, 4.6 Hz, 1 H), 1.80-1.46 (m, 3 H), 1.45-1.39 (m, 2 H), 1.37 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.8, 138.4, 128.8, 127.6, 127.1, 123.4, 76.4, 63.2, 35.1, 33.1, 26.4, 22.1, 20.6

CI-HRMS Calcd for $C_{13}H_{19}O_2$ $(M + H)^+$: 207.1385 Found: 207.1386

Anal Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.80; H, 8.83

2-(4-bromonaphthalen-1-yl)-2-methyltetrahydrofuran 19

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35-8.30 (m, 1 H), 8.24-8.16 (m, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.65 (d, *J* = 8.0 Hz, 1 H), 7.61-7.50 (m, 2 H), 4.07 (td, *J* = 8.0, 4.8 Hz, 1 H), 3.87 (dd, J = 8.0, 7.2 Hz, 1 H), 2.60-2.46 (m, 1 H), 2.45-2.34 (m, 1 H), 2.16-2.00 (m, 1 H), 1.94-1.81 (m, 1 H), 1.77 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.4, 133.1, 129.9, 128.7, 126.8, 126.4, 123.5, 122.6, 84.7, 67.1, 39.9, 30.1, 26.9

CI-HRMS Calcd for $C_{15}H_{16}{}^{79}BrO$ $(M + H)^+$: 291.0384, Found: 291.0385

Anal Calcd for $C_{15}H_{15}{}^{79}BrO$: C, 61.87; H, 5.19. Found: C, 62.94; H, 5.22

1,4-bis(2-methyltetrahydrofuran-2-yl)naphthalene 20

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30-8.22 (m, 2 H), 7.79- 7.72 (m, 2 H), 7.57-7.42 (m, 2 H), 4.07 (td, *J* = 8.0, 4.8 Hz, 2 H), 3.94-3.82 (m, 2 H), 2.62-2.49 (m, 2 H), 2.43-2.31 (m, 2 H), 2.14-1.99 (m, 2 H), 1.95-1.82 (m, 2 H), 1.78 (s, 6 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.1, 131.7, 127.3, 125.2, 122.4, 85.0, 67.1, 39.9, 30.2, 26.9

CI-HRMS Calcd for $C_{20}H_{25}O_2$ $(M + H)^+$: 297.1854. Found: 297.1851

Anal Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.26; H, 8.19

2-(4'-bromo-[1,1'-biphenyl]-4-yl)-2-methyltetrahydrofuran 21

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79-7.35 (m, 8 H), 4.15-4.00 (m, 1 H), 3.99-3.87 (m, 1 H), 2.35-2.16 (m, 1 H), 2.14-1.95 (m, 2 H), 1.94 1.76 (m, 1 H), 1.55 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.2, 140.3, 139.7, 132.2, 129.8, 129.1, 127.5, 127.3, 127.1, 125.7, 121.8, 84.5, 68.0, 39.9, 30.1, 26.2

CI-HRMS Calcd for $C_{17}H_{18}{}^{79}BrO$ $(M + H)^+$: 317.0541. Found: 317.0544

Anal Calcd for $C_{17}H_{17}{}^{79}BrO$: C, 64.37; H, 5.40. Found: C, 64.50; H, 5.45

4,4'-bis(2-methyltetrahydrofuran-2-yl)-1,1'-biphenyl 22

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, J = 8.4 Hz, 4 H), 7.45 (d, J = 8.4 Hz, 4 H), 4.12-4.00 (m, 2 H), 4.00-3.90 (m, 2 H), 2.33-2.19 (m, 2 H), 2.14-1.94 (m, 4 H), 1.93-1.80 (m, 2 H), 1.56 (s, 6 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.5, 139.5, 127.4, 125.5, 84.6, 69.5, 39.9, 30.1, 24.4

CI-HRMS Calcd for $C_{22}H_{27}O_2$ $(M + H)^+$: 323.2011. Found: 323.2015

Anal Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.70; H, 8.03

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4.7 Final conclusions and closing remarks

As outlined in section 1.8, the aim of the thesis was to investigate neglected areas of Heck chemistry and further develop existing ones into more efficient, cheap or useful processes. This was to be done by reaction optimisation, catalyst design and mechanistic investigation. Focussing on the reactions of electron-rich olefins such as enol ethers and unsaturated alcohols, three related but distinct projects were undertaken.

Chapter 2 describes the Heck reaction of electron-rich olefins with vinyl halides. Focussing specifically on the vinyl halides allowed us to discover some significant differences in their reactivity when compared to more common aryl halides. First, we established that a Pd-dppp catalyst could regiosectively vinylate enol ethers and other olefins internally in molecular solvents without the need to add halide scavengers or H-bond donating salts. This was somewhat surprising as additives of this type are usually needed when arylations are performed. Following this we undertook a ligand screening and found that monodentate ligands were, in fact, superior to bidentate. A Pd-dpppO catalyst allowed lower Pd loadings and higher rates of reaction, even with the less reactive 2-substituted vinyl ethers. Evidence gathered from a mechanistic study suggests that, for vinyl halides, the Heck reaction with electron-rich olefins proceeds via a neutral pathway. This led to the proposal of an alternative mechanism for the reaction and the conclusion that

vinyl halides can no longer be treated as analogous to aryl halides and by treating them separately new, more efficient catalytic systems have been developed.

Chapter 3 introduced a cascade reaction comprising a Heck arylation of butyl vinyl ether in alcohol solvents followed by cyclic ketal formation where the solvent alcohol is incorporated into the product. The reaction works with a range of aryl bromides and the corresponding cyclic ketals are obtained in good to excellent yields. In addition, changing the alcohol solvents allowed the direct synthesis of a variety of different cyclic ketal rings. This reaction not only allows the use of cheaper reagents but also provides a chemoselective (other carbonyl groups present) ketal formation in a basic environment. Some diols were unsuitable for the Heck reaction and so could not be used for the cascade reaction. Where this was not possible we found that the isolated enol ethers could be converted to the desired ketal by reaction with a diol in the prescence phosphoric acid catalyst. Under these conditions the previously unsuccessful diols reacted smoothly to form the ketals in good yields. The two methods presented provide a convenient route to cyclic ketals in a selective and high-yielding manner and by choosing the correct aryl bromide and diol, synthetically relevant intermediates can be produced.

Chapter 4 set out to utilise the Heck arylation of unsaturated alcohols in a one pot procedure for the synthesis of substituted THF′s and THP′s. Cyclisation of the internally arylated Heck products mediated by a brønstead acid was to lead to 2-aryl-2-methyl disubstituted oxygen heterocycles. Although we found a catalytic system similar to that in Chapter 3 was good for the arylation, the cyclisation in alcohol solvents failed and no desired product was obtained. Success was achieved by carrying out the Heck reaction in dioxane and adding H-bonding salts to control the

regioselectivity, addition of a co-solvent and HBF_4 after the arylation allowed the cyclised products to be obtained in good overall yields. THF's and THP's were obtained from a variety of aryl bromides and the procedure represents a convenient method of synthesis of these valuable compounds from readily available starting materials.

The author hopes that the work presented in this thesis has gone some way to expanding the scope of the Heck reaction of electron-rich olefins. Some questions have been raised by discovering features of the reactions that differ from conventional thinking and methodologies developed that have potential use in synthetic organic chemistry. Future work would hopefully see these questions answered and the reactions further developed and utilised in total syntheses of complex organic molecules.